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The Mechanism of Action of Penicillin*

HARRY EAGLE, M.D.

Bethesda, Maryland

THE FACT that the clinical management of infectious disease has been drastically altered with the advent of the antibiotics requires no elaboration. The strikingly reduced mortality of infections such as miliary tuberculosis, bacterial endocarditis, and rickettsial diseases; the prompt symptomatic relief and the accelerated cure in quite a number of other infections; the efficacy of the antibiotics as prophylactic measures: these factors add up to a radical change in our approach to the management of infectious disease. Over and above these clinical considerations is the enormous gain in human resources effected by the treatment of crippling infections such as yaws, world-wide in distribution and affecting millions of people; while the economic gain resulting from the growth-stimulatory effect of antibiotics in cattle, swine, and poultry has not yet been fully assessed.

The microbiologist must ruefully acknowledge that these striking achievements have not resulted from the slow, painstaking accumulation of basic observations, the usual pattern of important therapeutic advances. Almost without exception, the antibiotics have been obtained either by accident, or in the course of mass screening programs undertaken for that specific purpose. Further, not only has no important agent been arrived at inductively, on the basis of *a priori* considerations, but the mode of action of even one of these compounds has yet to be elucidated. This becomes all too evident in the following summary of the available information with respect to the mode of action of penicillin, the first antibiotic to find widespread use, and quantitatively still the most important.

Any discussion of the mode of action of a chemotherapeutic agent may be at two levels: in general terms, how does the agent effect cure in the infected host; and at the cellular level, what is its chemical effect on the bacterial cell?

THERAPEUTIC ACTION IN VIVO

I think we may now take it for granted that penicillin cures infections primarily because it kills bacteria. Although Miller and associates[1] have made the important observation that penicillin has a detoxifying effect on some bacterial toxins in the experimental animal, as yet no information is available as to whether this phenomenon contributes to its therapeutic effect in man. Now, to say that penicillin cures infection because of its direct bactericidal action is not to deny the importance of host factors in the eradication of the invading organism. Cure unquestionably usually is effected by the combined action of the drug and of the host defenses; but, at least with penicillin, those two mechanisms apparently operate independently. The antibacterial effect of the drug as such is not demonstrably potentiated by the host. The concentrations necessary to kill a given bacterial strain in vivo are precisely the same as those required

HARRY EAGLE, *a 1927 graduate of Johns Hopkins Medical School, is chief of the section of experimental therapeutics, National Microbiological Institute, National Institutes of Health, United States Public Health Service, Bethesda, Maryland.*

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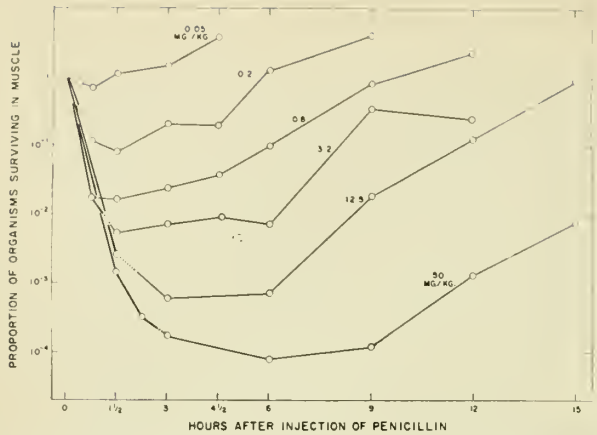

Fig. 1. Bactericidal action of penicillin on group A streptococci in a mouse muscle infection.

to kill the same organism in the test tube.[2] Those bacteria which are highly resistant in the test tube are equally resistant in the body. Also, the bactericidal action of penicillin persists only as long as the concentration at the focus of infection remains at effective levels. As soon as the concentration of penicillin at the focus of infection falls below the concentration which is effective in vitro, the bactericidal action usually stops (figure 1).[3a]

Conversely, there is no proof that penicillin regularly increases the capacity of the host to deal with an infection. It is true that in 1 of 4 experimental infections tested in this laboratory, produced by a group B streptococcus, the organisms which survived the action of penicillin were then more susceptible than normally to the host defenses and continued to disappear rapidly after the penicillin itself had fallen to ineffective levels.[3b] However, this was not observed in any

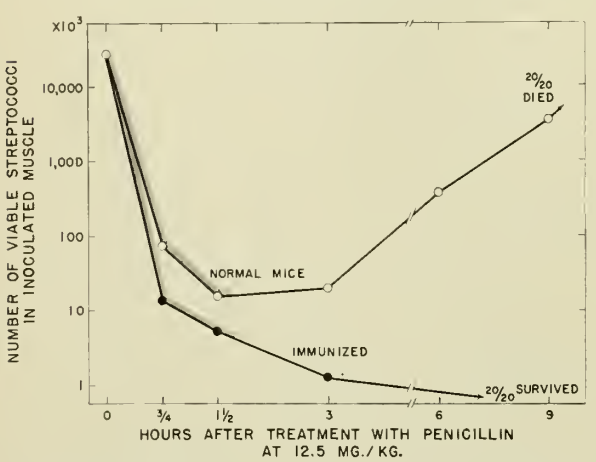

Fig. 2. Bactericidal action of a single dose of sodium penicillin G in normal and in immunized mice. Cross-hatched portion of curve indicates average time for which the serum concentration of penicillin remained in excess of the effective concentration.

of 3 other experimental infections tested, produced with group A streptococci, or type I or type III pneumococci. In those infections, as indicated in figure 1, there was no evidence that penicillin had increased the capacity of the host to deal with the invader.

In an experimental streptococcic infection in mice, the separate and mutually supplementary roles of penicillin and of the host defenses in the eradication of infections could be distinguished quite clearly.[4] In nonimmune mice, the bactericidal action of penicillin stopped as soon as the antibiotic had fallen below effective levels. The surviving bacteria then remultiplied to cause a uniformly fatal infection. In partially immunized mice, in which the degree of immunity was not enough to prevent a fatal infection after a large inoculum, the bactericidal action of penicillin proceeded at precisely the same rate and for exactly the same period of time as in the nonimmune mice (figure 2). The difference lay in the fact that after the penicillin had fallen to ineffective levels, the immune mechanisms of the host were then able to dispose of the few remaining organisms. What would otherwise have been a subcurative dose of penicillin was able to effect cure by virtue of the supplementary effect of the host defenses.

ANTIBACTERIAL ACTION OF PENICILLIN

1. *Theories as to mode of action.* If we accept the thesis that the therapeutic action of penicillin rests primarily on its direct bactericidal action, we come to the more difficult and more challenging question of what underlies that cytopathogenic effect. No satisfactory and conclusive explanation has yet been offered. On the basis of his extensive studies on bacterial amino acid metabolism, Gale[5] was led to suggest that the locus of action of penicillin was on the transport mechanism for glutamic acid; that penicillin-treated bacteria were no longer able to transport essential glutamic acid across the cell boundary. It now seems clear, however, that this is neither the regular nor probably the primary effect of the antibiotic. In at least two instances,[6,7] strains of bacteria have been found which do not require glutamic acid, in which there is therefore no necessity for glutamic acid transport into the cell, but which are nevertheless highly sensitive to penicillin. More recently Gale[8] found that under appropriate conditions, cell-free staphylococcic extracts are able to synthesize protein, and in that cell-free system, penicillin at a relatively low concentration (1μg/ml) inhibited the formation of an adaptive enzyme, galactosidase, as well as the synthesis of ribonucleic acid.

Whether a similar interference with synthetic processes is the basis of its antibacterial action, and, if so, which component of the synthesizing systems is the precise locus of attack, remain to be determined. In this connection Hotchkiss[9] observed that in suspensions of penicillin-treated staphylococci, peptides accumulated in the outside medium, also indicative of a derangement of protein metabolism. Further, Park and Johnson[10] found that penicillin-treated staphylococci accumulated abnormal uridine phosphates, suggesting an effect on nucleic acid metabolism.

Penicillin has been reported to have a number of other metabolic effects. Some of these are observed only at concentrations so high, for example, 1,000 to 10,000 μg/ml, that they are almost certainly not related to its bactericidal effect at concentrations of 0.1 to 1 μg/ml. Also, in many instances difficulty arises in distinguishing between a biochemical effect due directly and primarily to the antibiotic, and a secondary effect in a dying cell which is not directly related to its action.

2. *Importance of the physiologic state of the organism.* One of the very earliest observations with respect to penicillin action remains one of the most important and most tantalizing – the fact that penicillin kills bacteria in vitro only if the bacteria are in an environment which permits active metabolism and growth.[11,12] In vivo also, organisms in a locus unfavorable for growth are relatively invulnerable to the drug (figure 3).[13] The fact that the physiologic state of the bacteria thus conditions the action of penicillin may have important implications in its clinical use. Quite possibly at least some of the unexplained and anomalous treatment failures observed with penicillin may be due to the fact that there are foci of infection in which the organisms are in an unfavorable environment, and for that very reason are paradoxically refractory to its antibacterial action.

This phenomenon is obviously relevant to the mode of action of penicillin, but precisely what underlies it is not clear. Does it mean that penicillin can only react with a growing, metabolizing cell, and that the so-called resting cell is not able to combine with the antibiotic? On the basis of studies with radioactive penicillin, to which I will refer later, the answer is in the negative. Resting bacteria, and indeed, bacteria suspended in salt solution, or cell-free extracts of bacteria, combine with the antibiotic just as avidly as do organisms in the logarithmic phase of growth. How then can the fact be explained that penicillin affects only actively metabolizing bacteria? It is conceivable that penicillin blocks

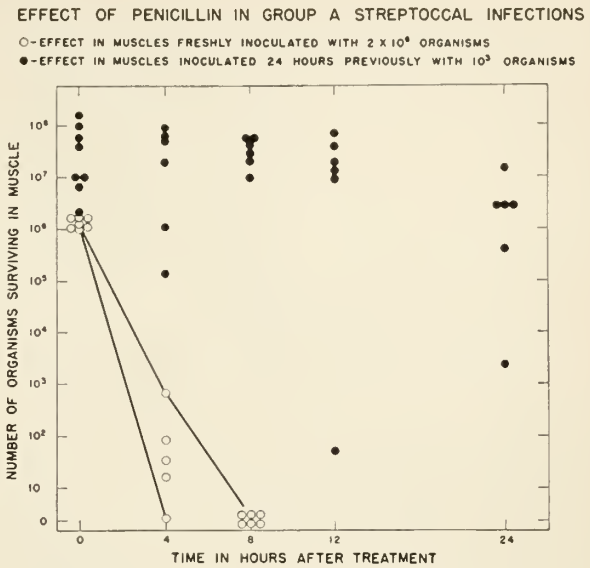

Fig. 3. Effect of age of infection on therapeutic efficacy of penicillin. Contrasting, in same animal, bactericidal action of penicillin in a freshly inoculated muscle (o-o) and in a muscle inoculated 24 hours previously (●-●).

a metabolic reaction and thereby leads to the accumulation of a metabolite which is toxic in excess. That accumulation would occur only in the actively metabolizing cell.[14]

As a second possibility, let us assume that penicillin prevents this reaction by actually combining with the enzyme protein which mediates it. In the resting cell nothing more happens; and, if the penicillin is removed or if the cells are placed in a fresh medium, they resynthesize the enzyme affected, and the cell resumes its normal metabolic activity. If, however, the organisms are exposed to penicillin in a growing medium, then after penicillin has inactivated the postulated vulnerable and essential enzyme, the cell may attempt to replace it by synthesizing new enzyme from precursor substances in the cell. The newly formed enzyme would then also be inactivated, and this would continue until the cell had exhausted the precursors, whereupon the cell would become nonviable.

These are only two of a number of possible explanations for this interesting and important observation.

3. *The zone phenomenon.* Another puzzling aspect of penicillin action is the fact that with some bacterial species, high concentrations of penicillin are less rapidly effective than a lower, optimal concentration.[15] This is not too important clinically. At worst, even if the same phenomenon did occur in vivo, it would mean that excessively large doses of penicillin would kill bacteria more slowly than the lower concentrations afforded by lower doses. It would be most

inadvisable for the physician to attempt to circumvent this zone phenomenon, and to provide precisely the optimal concentration at the focus of infection. For a number of reasons, such attempts would not succeed, and there would be the real risk of inadequate dosage.

However unimportant the zone phenomenon may be in the treatment of infection, it is highly pertinent in relation to the mode of action of the drug, and possible explanations have been discussed in detail elsewhere.[14]

4. *Binding of penicillin by bacteria.* The use of radioactive penicillin has made possible an important advance in our understanding of the reaction between penicillin and bacteria. As a result of such studies,[16–18] a number of conclusions may now be drawn with respect to the actual combination between penicillin and bacteria. If a suspension of bacteria is exposed to radioactive penicillin under standard conditions and if, at varying periods after that exposure, the bacteria are centrifuged out, washed, and their radioactivity measured to determine the amount of penicillin with which they have combined, penicillin is found to be rapidly bound and concentrated, and that the more sensitive the strain, the more readily it enters into combination with the antibiotic. A sensitive organism may concentrate the antibiotic as much as 200-fold. This is not observed with penicilloic acid, or other degradation products of penicillin. The correlation between sensitivity and the ability to combine with penicillin (figure 4) is good enough to suggest a causal relationship, that is, that it is the combining affinity with penicillin which actually determines the sensitivity of the cell. These differences in the amounts of penicillin bound are not due to differences in permeability; for in cell-free extracts, large molecular weight components of the cell also combine with penicillin and again in relation to the sensitivity of the cell. A reasonable working hypothesis is that the combining affinity of the cell for the antibiotic determines its sensitivity. There is an interesting corollary to this thesis. It would follow that all bacteria are equally sensitive to penicillin, in the sense that a given amount of bound penicillin has the same effect on all cells, sensitive and insensitive alike. The difference between a penicillin-insensitive organism such as Escherichia coli and a highly sensitive organism such as Streptococcus pyogenes would be in the amount of penicillin which must be added to the outside fluid in order to effect the same lethal degree of combination.

This has actually proved to be the case. At lethal concentrations all of the strains studied

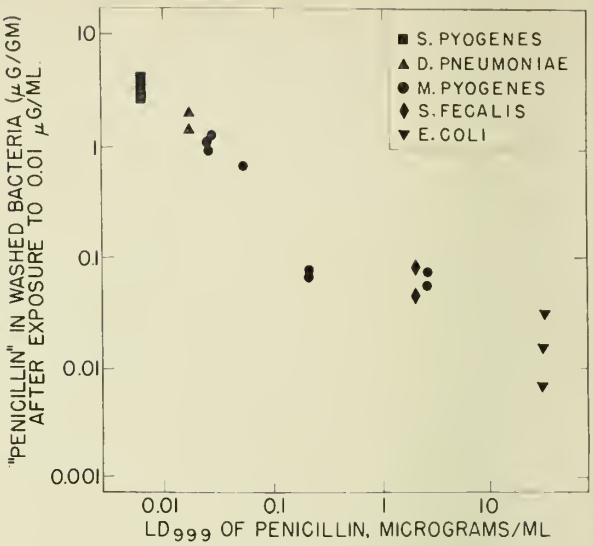

Fig. 4. Amounts of radiopenicillin bound by bacteria of varying sensitivity from a solution containing 0.01 μg. per ml.

were found to have bound the same amount. From 900 to 1,250 molecules of penicillin can be bound per cell without any demonstrable effect on the rate of growth. A slight increase in the bound penicillin, up to 1,500 to 1,700 molecules per cell, results in a bacteriostatic effect. With further increase in the bound penicillin the cells begin to die, and the most rapid bactericidal action is effected when the cell has combined with 1,500 to 4,000 molecules.[18d] These observations suggest that all bacteria contain one or more penicillin-vulnerable components capable of combining with 1,500 to 4,000 molecules of the antibiotic per cell; that as much as ⅓ to ⅔ of those penicillin-avid components can be inactivated without any demonstrable effect on cell function; and that death results when those penicillin-vulnerable components are almost saturated with the antibiotic. In the penicillin-sensitive cells, those components are highly reactive; in the insensitive cell, they have a low order of reactivity. To repeat, the only difference between, for example, E. coli and S. pyogenes lies in the amount of penicillin which must be added to the outside fluid in order to effect this lethal degree of combination.

Most discussions of the reasons for the varying resistance of bacteria to antibiotics have emphasized possible differences in the permeability of the cells, differences in the degree and rate at which penicillin is inactivated by the cells, or differences in the metabolic requirements of the organisms. The data here presented suggest that the varying penicillin resistance of bacterial strains in nature usually depends on none of these factors, but instead rests on a difference

in the reactivity of penicillin-vulnerable component or components of the cell with the antibiotic. On this basis, cells equally permeable to the drug, equally unable to destroy it, with similar metabolic requirements and similar metabolic pathways, could nevertheless vary widely in their resistance to the drug. This concept is not new, but was first clearly enunciated by Ehrlich, who fifty years ago suggested that differences in cell susceptibility to drugs may depend on the varying reactivity of the protoplasm of the cell with a cytotoxic agent.

I regret to say that our attempts to isolate and characterize this penicillin-reactive component have to date been unsuccessful.

5. *Penicillin resistance.* Intimately related to the mode of action of penicillin, and to the binding phenomenon which I have just discussed, is the development of resistance to penicillin. As Dr. Spink and his associates at the University of Minnesota were among the first to recognize, it is important to distinguish sharply between two kinds of penicillin resistance: (a) the "natural" differences in resistance observed between different bacterial species and between different strains of the same species; and (b) the resistance which may be developed by a sensitive strain after exposure to the drug. Let us consider first the question of natural resistance. At least 3 quite different mechanisms are here involved. Some strains produce a penicillinase, which inactivates the antibiotic in the surrounding medium before it can reach the bacteria. This mechanism is self-explanatory and requires no discussion. Second, the use of radioactive penicillin has made it possible to show that certain bacterial strains, which do not release a penicillinase in the medium, are nevertheless able to degrade penicillin after it enters the cell.[19] If these strains are exposed to the antibiotic and then extracted, the extracts may be highly radioactive but are completely devoid of penicillin activity; while with strains which do not have this capacity to degrade the intracellular penicillin, the radioactive sulfur content of the cell extract corresponds reasonably well to its penicillin activity.

However, these 2 mechanisms of penicillin destruction outside or inside the bacterial cell account for only a small proportion of the naturally penicillin-resistant bacteria. By far the most important single factor determining the sensitivity of bacteria to penicillin is the widely varying affinity of the penicillin-vulnerable component for the antibiotic, as discussed earlier.

Let us now turn to acquired resistance, that which can be produced in any organism by serial transfer through antibiotic. A number of workers have attacked the problem of whether originally sensitive bacteria become resistant by virtue of rare and spontaneous mutations which then grow out selectively, or whether instead a directed adaptation of the organisms to the drug occurs, the induction by the environment of a heritable change in the bacteria. Suffice it to say that almost all the experimental evidence supports the former view, that the change from sensitivity to resistance, when it occurs, reflects a spontaneous mutation and the selective multiplication of that rare mutant in the presence of the antibiotic.

Let us instead consider the reasons for the increased resistance observed after the selective propagation of originally sensitive bacteria in penicillin. Surprisingly, none of the 3 factors known to be responsible for differences in natural penicillin resistance applies to these resistant variants. These hot-house variants do not produce penicillinase, nor do they have the capacity to destroy penicillin after it enters the cell. Furthermore, these resistant offspring of originally sensitive strains often have the same high combining affinity with the antibiotic as the parent sensitive strain and sometimes are even more reactive.[18b] Unfortunately there is no present clue to the mechanism of the resistance produced by selective transfer of originally sensitive bacteria in increasing concentrations of antibiotic.

6. *Reactivity of mammalian cells with penicillin.* The miraculous aspect of the antibiotics is not that they kill bacteria, but that this is usually accomplished without killing the host. On the basis of the foregoing discussion, there are a number of possible explanations for the resistance to penicillin of human and animal tissues. The antibiotic may not be able to get into the cell. If it does, it may be inactivated as fast as it enters. If it is not inactivated, it may have a low combining affinity with those components which in bacteria are vulnerable to penicillin. Finally, by virtue of qualitative differences in metabolic pathways, these specific components may not be present or may not be essential in the mammalian cell. To consider those possibilities in order, penicillin does enter mammalian cells. On exposure to radioactive penicillin, both mouse fibroblasts and human carcinoma cells were found to contain an amount of radioactive material consistent with a simple diffusion equilibrium between the intracellular fluids and the surrounding medium.[18c] Further, the intracellular penicillin is not inactivated. When the cells were extracted after their exposure to the antibiotic, the radioactive material which was with-

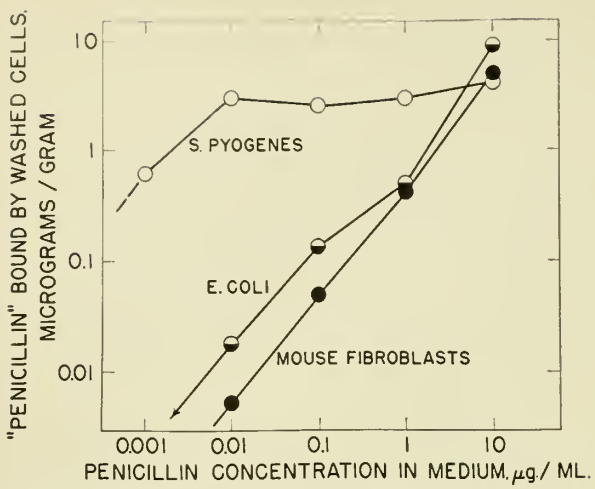

Fig. 5. Penicillin bound by mouse fibroblasts, and retained after washing, as compared with binding by illustrative penicillin-sensitive (Streptococcus pyogenes) and penicillin-insensitive (Escherichia coli) bacteria.

drawn from the cells was as actively bactericidal as penicillin, and was presumably the unaltered antibiotic. It follows that these cells either do not contain a penicillin-vulnerable component, or, if they do, that this component has a very low order of reactivity with the antibiotic. In fact, these two cells were found to combine with penicillin even less actively than, for example, E. coli (figure 5); and this degree of binding is no more than would be obtained with a degraded material such as penicilloic acid. To repeat, mammalian cells are resistant to penicillin either because they do not contain penicillin-vulnerable components, or because those components have a very low order of reactivity.

CONCLUSION

Our understanding of the mechanism of penicillin action lags far behind its practical application in the treatment of disease. This unfortunately is not peculiar to penicillin, but is part of a general recent pattern. A number of therapeutic agents of unparalleled activity have been discovered, either by accident or as the result of empiric screening programs. These agents have not come about as the result of studies of cell function; and even now, after years of successful use in millions of cases, the mechanism of their action is unknown. Let us, however, not conclude that the study of the effects of drugs on cellular function is unimportant, even if that approach has to date been relatively unrewarding at a pragmatic level. The detailed exposition of how these extraordinary agents bring about the death of the cell will contribute materially to our understanding of cellular function, both bacterial and mammalian, and could conceivably lead to more effective treatment.

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Recent Trends in Dermatologic Therapy

FRANK M. MELTON, M.D.
Fargo, North Dakota

THE PACE of progress moves with increasing rapidity. Each year we find it more difficult to keep up with not only what is new, but more important what is of value. Tremendous amounts of money, time, and effort go into the production of new drugs. Unfortunately, many fail to find a place of permanent value.

John Downing[1] has very aptly pointed out that "The literature is extremely confusing. Many reports are published as the result of enthusiasm aroused by the relief of a few patients with a given substance. The drug is too readily distributed by commercial houses and if the cure is not corroborated, the negative results are seldom published by subsequent investigators. As the result, the product continues on the market at great expense and with little value to sufferers."

An example of this situation was the treatment of psoriasis with undecylenic acid. In 1949, several reports of this treatment appeared. In 1951, Herbert Rattner[2] conducted a survey by sending questionnaires to 75 dermatologists throughout the country. Their reports on the experience of treating 1,100 cases were decidedly unfavorable. Not only was the drug ineffective, but a number of reactions were reported, some serious in nature.

The point is, a few questions must be asked about these new products when they are presented to us as Downing[1] suggests: "First, what is its advantage over accepted therapy? Has it demonstrated definite bactericidal activity in vitro and is this activity maintained at various temperatures? Does the drug diffuse readily from its ointment bases? How much of the medication is absorbed by the skin? Is it more economical than the accepted medication? If it is expensive, is its cost justified because of the reduction in time of disability and suffering? Is it a sensitizer? Does its use in more or less unimportant local infections sensitize patients and preclude its use in more systemic diseases? All these factors must be considered."

FRANK M. MELTON, *a 1939 graduate of the University of Louisville School of Medicine, is on the staff of St. John's and St. Luke's hospitals, Fargo; and St. Ansgar's Hospital, Moorhead, Minnesota.*

CORTISONE AND ACTH

When cortisone and ACTH first became available, they were widely used in an endeavor to discover just what could be expected of them. Experience with their use is now sufficient to give a more critical evaluation of their place in dermatologic therapy. While these drugs have been shown to have very definite assets, they also have limitations and liabilities which must be considered. Although opinions of investigators of equal knowledge and ability differ as to the precise indication for these drugs, the trend is toward conservative use in those conditions in which they have proved of value. It must be remembered that these medicines do not cure the conditions for which they are used, but merely depress the activity of the condition and minimize the symptoms.

Paul O'Leary and John Erickson[3] of the Mayo Clinic in an article on the "Use and Abuse of Cortisone and ACTH" gave the following indications for these drugs. First, to extend the life expectancy of otherwise fatal conditions such as acute systemic lupus erythematosus and pemphigus. Second, to tide the patient over in acute self-limiting inflammatory dermatoses such as urticaria, drug eruptions, angioneurotic edema, and erythema multiforme, conditions which do not respond to more conservative therapy.

A third group of chronic dermatoses in which the drugs are only exceptionally indicated includes neurodermatitis, dermatomyositis, psoriasis, dermatitis herpetiformis, seborrheic dermatitis, obscure chronic contact dermatitis, anogenital pruritus, and similar common stubborn dermatoses. While cortisone and ACTH may produce considerable temporary improvement, the conditions often recur on termination of therapy, thus requiring prolonged high doses with treatment complications.

When using these drugs, it is important to be sure the patient understands that he is still sick even though his symptoms are relieved.

HYDROCORTISONE OINTMENT

Cortisone has been used in an ointment, but was not very effective on the skin. Recently hydrocortisone ointment has become available. While it has been in use for too brief a time to determine its ultimate status, there are indications that it will be effective in a number of dermatoses. Good results have been reported in atopic dermatitis (infantile eczema), eczema of the eyelids, nipple, and ears; pruritus of the anus, scrotum, and vulva; and in localized neurodermatitis. Reports have been only fair in seborrheic dermatitis and intertriginous psoriasis. It has not been of value in psoriasis, lichen planus, alopecia areata, and scleroderma.

The big problem is the cost of this product. One hesitates to prescribe a medicament which costs $3.00 to $6.00 for a very small quantity, especially when it may not prove effective. Many investigators feel that the 0.25 per cent preparation is the optimum dose and is justified in spite of the extra cost. Usually after 1 tube is used, its value can be determined. If effective, the less expensive and less concentrated preparation may be tried. Sensitization reactions or systemic effects have not occurred from the use of the drug to date, even when used on extensive areas of damaged skin for long periods.

ANTIBIOTIC OINTMENTS

Until the advent of the sulfonamides and antibiotics, pyogenic infections were a big dermatologic problem. The sulfonamides are now seldom used as ointments, not because they aren't effective, but because of the relatively high incidence of allergic reactions. While the sensitization reactions due to penicillin are not as severe, more and more are occurring. For this reason, the use of penicillin ointment is contraindicated, since these sensitizations will prevent its later use for more serious systemic infections.

While all the newer antibiotics have a place in the treatment of cutaneous infections, depending on the type of organism and its susceptibility to the medication, the factor of sensitization mentioned before must be kept in mind. Although the rate of sensitization to Aureomycin, Terramycin, Erythromycin, and other antibiotics used systemically has been much less than with penicillin, their continued use on the skin may result in a similar high rate of sensitivity. For this reason, those antibiotics which are rarely used internally are preferable, such as neomycin, bacitracin, and polymyxin B.

For a single topical antibiotic, neomycin has the advantage of stability at room temperature even in solution. However, it is not as effective against streptococcic infections as bacitracin, and secondary growth of monilia occasionally occur. Bacitracin is stable for only short periods of time when in solution or in water-soluble bases and must be kept refrigerated. When single antibiotics are not effective, combinations such as neomycin and bacitracin, bacitracin and polymyxin B, and other combinations may be tried. Sensitivity studies may also be helpful in indicating the proper antibiotic to use.

FUNGOUS INFECTIONS

The treatment of superficial fungous diseases still leaves much to be desired. An exasperating situation occurs when the fungus does not penetrate the living tissue, but is found in the dead layers of the skin. One would think that a little judicious use of sandpaper or a wire brush would suffice for its eradication. One investigator went to the ultimate in therapy in an effort to cure a fungous infection of the hands of one of his patients.[4] Fortunately, fungous infections of the hands are rare, a fact that still is not sufficiently recognized. In this instance, the patient applied 5 per cent sodium sulfide to his hands each night and then an ointment containing 10 per cent caprylic acid and 10 per cent formalin in Carbowax and then covered his hands with rubber gloves. At the end of six months, the patient refused further therapy and the fungus was still present. The salicylanilide compounds, undecylenic acid-propionic acid compounds, and conventional peeling preparations are most widely used.

Another type of ringworm of the scalp is now spreading across the country from Mexico, Texas, and California. It differs from the audouini infections in that the hairs do not fluoresce under the Wood light. The only sure methods of diagnosis are cultures and microscopic examination of the hairs and stubs. Approximately 5 per cent of the infections occur in adults. The most striking feature is the great variability of the clinical picture. In some it may appear as seborrhea or even simulate chronic lupus erythematosus, while in others it may appear as a pustular eruption or granuloma of the scalp. I have 2 cases, Mexican children who visited Mexico just prior to the infection.

SYSTEMIC FUNGOUS INFECTIONS

The systemic fungous infections have always been a serious problem because they are almost invariably fatal. While cutaneous blastomycosis is not always fatal, the lesions usually persist for years.

In recent years a very interesting series of

events has occurred. At the Liverpool School of Tropical Medicine, a number of investigators studied a group of compounds known as aromatic diamidines in a search for a cure for trypanosomiasis in Africa. One of the compounds they studied, stilbamidine, was also effective in the treatment of leishmaniasis. Later it was found to inhibit the growth of bacteria but was not as effective as the sulfonamides and penicillin. In 1945, Elson[5] studied the effect of propamidine, another of these compounds, on a series of fungous cultures. He found that the organisms causing blastomycosis and sporotrichosis were greatly inhibited. No clinical application of these findings were made for several years. In July 1952, Schoenbach and associates[6] reported the successful treatment of systemic blastomycosis with stilbamidine. In December 1952, Curtis and Harrell[7] reported 2 cases successfully treated with stilbamidine and 2 cases treated with diethylstilbestrol, compounds which are chemically related.

The last 2 patients had inoperable carcinomas of the prostate and were receiving diethylstilbestrol. They also had blastomycosis. On return visits, it was noted that these lesions were healing and no other therapy was given. At the end of three months, the lesions had healed.

CHEMOSURGERY—CANCER

A very interesting technic for the treatment of skin cancer has been developed by Dr. Frederick Mohs of the University of Wisconsin. This method has the advantage of microscopic control of the excision of the lesion. While the technic is not suitable for general use, it offers another approach in difficult cases.

Briefly the technic is as follows: A thin layer of a paste containing zinc compounds is applied to the lesion for twenty-four hours. During this time the zinc chloride penetrates the tissues and fixes them. The depth of penetration is controlled by the thickness of the layer of paste. The tissue is excised in horizontal layers just within the fixed area, making it a painless and bloodless procedure. An outline of the entire lesion is drawn on paper about twice the actual size and as each piece of tissue is excised, it is indicated on the map, numbered, and the edges are colored with dyes. The tissue is then placed upside down on a freezing microtome and sections are cut from the under surface. Then these sections are stained and placed on slides which are examined and the areas containing epithelioma are indicated on the map and are retreated until the epithelioma is completely removed.

Results have been excellent. In a series of 291 basal-cell epitheliomas of the face, Dr. Mohs experienced a 96.2 per cent five-year cure rate.[8] The five-year cure rate for 136 squamous epitheliomas of the face was 85.6 per cent, in spite of the fact that many were far advanced, and over one-third had recurred after previous surgical or radiation treatment. The method is conservative, since only 1 or 2 mm. of tissue is removed beyond the point of actual carcinomatous invasion. In a group of 20 melanomas, the five-year cure rate was 35 per cent, which compares very favorably with more radical methods of therapy.[9] The important point that these studies show in relation to conventional surgical and roentgen therapy is the amazing extent to which these lesions can penetrate undetected under the skin and the need for adequate areas of excision and irradiation.

CHRONIC LUPUS ERYTHEMATOSUS AND LIGHT-SENSITIVE ERUPTIONS

Another new development has been the use of quinacrine hydrochloride (Atabrine) in the treatment of chronic discoid lupus erythematosus. While this condition is not a serious systemic disease, it has been a therapeutic problem. In 1951, Page[10] published the first paper on the treatment of lupus erythematosus in the English-speaking world. Since then, many investigators have studied the disease with good results.[11] However, Atabrine is not entirely free of serious reactions. The skin becomes yellow and is sometimes misdiagnosed as jaundice. Various forms of drug eruptions, aplastic anemia, and other hematopoietic reactions have occurred.

In the search for a less toxic drug for the treatment of malaria, chloroquine (Aralen) was found to be of value, not only for malaria, but chronic lupus erythematosus and light-sensitive eruptions.[12,13]

It is important to point out that these drugs should not be used in patients with acute or subacute systemic lupus erythematosus. Kierland and associates[11] reported reactions in all of the patients treated who had systemic lupus erythematosus.

PLANTAR WARTS

New treatments for warts appear each year. A recent method consists of injecting novocain into the base of the wart. Branson and Rhea[14] reported a 73 per cent cure rate in their series of 48 cases treated in such a manner. Important points to observe are that the needle should penetrate through normal skin to the base of the wart and no farther, and only one needle puncture should be made. Explanation of the pos-

sible mechanism is the production of ischemic necrosis.

The high rate of cure is still to be corroborated. The opinions of the dermatologists with whom I have discussed the procedure ranged it from "worthless" to "let's wait and see." My personal experience has been disappointing, although I have had a few cures.

HERPES ZOSTER

Several years ago the "new" treatment for herpes zoster was Aureomycin and Chloromycetin. In spite of the insistence of virologists and other investigators that "the favorable results of antibiotic treatment of viral diseases were due to the effect on associated bacterial infection and not on the virus,"[15] many papers appeared extolling the effect of these drugs on herpes zoster.

Further information on this subject has been revealed by two controlled studies. Kass and associates[16] treated 25 cases with Aureomycin, 25 cases with Chloromycetin, and 22 cases with aspirin, Phenacetin (acetophenetidin), and caffeine. Neither Aureomycin nor Chloromycetin hastened healing more than the analgesic. In three-fourths of the cases the lesions were healed in two weeks regardless of the type of treatment. A similar study by Schaffer and Svendsen[17] revealed the same results.

Cortisone has been advocated by some for the treatment of herpes zoster, although Kupperman and associates[18] have reported instances in which 3 patients developed herpes zoster while taking cortisone for rheumatoid arthritis. Some feel that although cortisone is not effective in treatment of the herpetic eruption, it is effective in treatment of postherpetic pain.

Vitamin B_{12} has also been used in the treatment of herpes zoster. Experience of the men with whom I have discussed its use has been that the course of the eruption is not altered, but that such treatment does relieve the pain and neuritis.

PROTECTIVE CREAMS

The development of "protective creams" containing silicone has been one of the recent advances in dermatologic therapy. At present, the following 3 compounds are available commercially: (1) Silicote—30 per cent silicone in petrolatum, (2) Pro-Derna—52.5 per cent silicone in bentonite base, and (3) Covicone—25 per cent nitrocellulose—castor oil intermediate, 2 per cent silicone.

These preparations offer some protection against greases, mineral oil, irritant dusts, and water soluble irritants and allergens, including soaps, detergents, alkalies, acids, chromates, formalin, and so forth. They afford protection against discharges from rectum, vagina, urethra, colostomies, and fistulas.

They are used to prevent contact dermatitis due to soap, detergent, and water soluble allergens; prevent diaper dermatitis; treat chapped lips and angular stomatitis; and protect the skin from discharges.

It must be remembered that these preparations are protective and not therapeutic and must not be used on skins which are acutely inflamed or infected.

Opinions differ concerning the relative values of these products. John Shaw[19] of the University of Michigan found that the most effective protective ointment against soap and water washings and exposure to soluble cutting oil washings was Silicote. This preparation was also more effective and cosmetically more acceptable than Pro-Derna. All the other ointments including Covicone were found to be of no value against these solutions.

Suskind[20] reported that Pro-Derna and Silicote were found effective against a wide range of aqueous irritants and sensitizers including mineral oils, alkalis, salts, formaldehyde, soluble machine coolants, and some alcohols. The silicone bentonite mixture was effective against mineral oils, as in cutting oils, while the petrolatum mixture was not. Covicone did not have as wide a range of effectiveness as Pro-Derna and Silicote, and cannot be regarded as a silicone protectant since its silicone content is so meager."

Edmund F. Finnerty, Jr.[21] reported he observed that Pro-Derna can protect 63 per cent of cases in which dermatitis could otherwise most certainly occur. His experience with the 30 per cent silicone in petrolatum confirms it to have good protective value against urinary, rectal, and vaginal discharges and from drainages from colostomy, fistula, and decubitus ulcers. He found that it was of little value against oil-soluble industrial irritants. Its film is excessively "greasy" on the hands and interferes with their use. The plasticized nitrocellulose-castor oil formulation, containing 2 per cent silicone, was of very little value as a protective for the limited number of patients on whom it was tried.

George Morris[22] concluded that protective creams—silicone and others—used by industrial workers have failed to prevent cutting oils from irritating the skin.

C. Conrad Smith and associates[23] used graded dilutions of a variety of common allergens and employed the open skin test method. Varying degrees of protection were demonstrated in 30

of 36 subjects who had previously prepared the skin test areas with Covicone. In comparing Covicone with 3 other protective skin preparations, 1 containing silicone, Covicone was found superior when the site of application was washed before the skin tests were applied.

In closing, I would like to mention a recent decision of the Council on Pharmacy and Chemistry[24] to omit antihistamine creams from New and Nonofficial Remedies. This action was taken after polling the opinion of some of the leading dermatologists from various sections of the country. The council concluded that although some of these creams apparently have been helpful in relieving some types of pruritus, the risk of contact dermatitis now overshadows their possible efficacy and further evidence is required to establish their usefulness.

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Neurotic persons with personality structures based on infantile conflicts are particularly prone to chronic disseminated neurodermatitis. Claude E. Fiske, Ph.D., and Maximilian E. Obermayer, M.D., of Los Angeles observe that such patients differ from other individuals with neuroses primarily by preoccupation with and erotization of the skin and to a lesser extent by such traits as guilt, hostile-dependent relationships, masturbation, and needs for self-punishment and exhibitionism. For these subjects the skin constitutes an uncertain barrier between self and baneful environmental forces.

Claude E. Fiske, and Maximilian E. Obermayer: Arch. Dermat. & Syph. 70:261-267, 1954.

Present-day Treatment of Mammary Carcinoma in the Female

F. HENRY ELLIS, JR., M.D.

Rochester, Minnesota

For the past sixty years radical mastectomy has been a widely accepted form of treatment for carcinoma of the breast. Unfortunately, the mortality rate from this disease has not declined appreciably in spite of improvements in surgical technic, early diagnosis, and ancillary procedures, such as roentgen and endocrine therapy. For this reason, radical mastectomy has recently come under attack from several quarters.

On the one hand are those who claim that radical mastectomy is an incomplete operation. They propose superradical operations in an attempt to encompass more of the lymphatic drainage.[1–7] On the other hand are those who suggest that the operation should be less radical and simple mastectomy and roentgen therapy should be relied on for definitive treatment.[8–16] Although sufficient time has not elapsed for final evaluation of either proposal, the rationale behind them must be examined and evaluated.

HISTORICAL ASPECTS[17]

Classical radical mastectomy as performed today with minor individual modifications involves adequate removal of the skin in the region of the lesion, complete dissection of axillary lymph nodes, and resection of the pectoralis minor and all but the clavicular portion of the pectoralis major muscle. The breast, overlying skin, muscles, lymph nodes, and node-bearing fascia must be removed en bloc.

Jean Louis Petit in 1774 believed that the roots of cancer were the enlarged lymph glands. For this reason, he advised and practiced their removal along with the pectoral fascia and portions of the pectoral muscles themselves when they were involved. Charles Moore in 1867 advocated removal of the entire breast in association with the axillary lymph nodes. Samuel Gross in 1880 brought Moore's teaching to this country and extended the operation to include removal of the pectoral fascia. Portions of the pectoral muscles were resected by Volkmann in 1875 and Heidenhain in 1889 in cases of advanced carcinoma of the breast.

Although over the years various surgeons had proposed the various components of the radical operation, Halsted brought these thoughts to culmination in the radical operation that he first described in 1894.[18] Halsted's main contribution was the complete axillary dissection which was made possible by routine removal of the pectoral muscles. In his first report, 50 cases of carcinoma of the breast were described in which the pectoralis major was routinely removed. In the same year, Willy Meyer[19] described a similar operation which included removal of the pectoralis minor muscle, a step later adopted routinely by Halsted.

Prior to the development of radical mastectomy, few patients with carcinoma of the breast were cured. The incidence of local recurrence varied from 51 to 82 per cent in reported series.[18] Only 6 per cent of Halsted's original 50 patients had evidence of local recurrence at the time of his report. Although a longer follow-up study of these early patients as well as later patients operated on at the Johns Hopkins Hospital revealed local recurrence in 32.2 per cent, the improvement over earlier methods of treatment was striking.[20]

The basic principles of the surgical treatment of carcinoma of the breast have changed little since Halsted's contribution sixty years ago. However, concepts regarding selection of patients for operation have changed, minor technical variations have been made, and newer methods of treatment including roentgen and endocrine therapy have been developed.

PRESENT STATUS AND STATISTICAL REVIEW

Selection of patients for operation. Survival statistics for patients operated on can be greatly improved by restricting the use of the operation to favorable cases. Haagensen's and Stout's criteria for the so-called categorically inoperable patient[21] (table 1) have had wide influence, although some surgeons have objected to re-

F. Henry Ellis, Jr., *a 1944 graduate of Columbia University College of Physicians and Surgeons, is instructor in surgery in the Mayo Foundation and consultant, section of surgery at the Mayo Clinic.*

TABLE 1
CARCINOMA OF BREAST: CRITERIA OF INOPERABILITY

1. Carcinoma developing during pregnancy and lactation
2. Extensive edema of the skin over breast
3. Satellite nodules in skin over breast
4. Intercostal or parasternal nodules
5. Edema of arm
6. Proved supraclavicular metastasis
7. Inflammatory type of carcinoma
8. Distant metastasis
9. Any two or more of the following signs of locally advanced carcinoma:
   a. Ulceration of skin
   b. Edema of skin of limited extent
   c. Fixation of tumor to chest wall
   d. Presence of an axillary lymph node measuring 2.5 cm. or more in transverse diameter and proved by biopsy to contain a metastatic lesion
   e. Fixation of axillary lymph nodes to the skin or deep structures of the axilla if node is proved by biopsy to contain a metastatic lesion

stricting use of the operation in such a manner.[22] In support of their concept, Haagensen and Stout[23] have shown that surgery may actually shorten the life of patients with advanced disease. Tomlinson and Eckert[24] and Wells[25] reported no five-year survivors among patients with categorically inoperable carcinoma of the breast subjected to radical mastectomy with the exception of a few patients who were either pregnant or lactating. Harrington[26] in 1937 showed that the prognosis for this group of patients is far from hopeless if operation is carried out before axillary metastasis has occurred. As a result, Haagensen and Stout[23] no longer classify such patients as categorically inoperable although they have no five-year survivors in their group. They have further amended their criteria to include among patients with categorically inoperable carcinoma those patients with either a histologically involved supraclavicular or internal mammary node. They now advocate routine biopsy of these areas prior to radical mastectomy when axillary nodes are clinically involved or when the lesion is centrally or medially located, thus further restricting use of the operation.[27]

Technical considerations. Various technical changes in the operation have been proposed from time to time. Neuhof[28] and Macdonald[29] have proposed routine resection of the axillary vein. Methods to reduce the incidence of postoperative lymphedema include use of muscle flaps and laminated gelfoam rolls to protect the axilla and splint the axillary vein.[30] Because of the relatively high incidence of nonsimultaneous bilateral carcinoma of the breast,[31,32] certain investigators including Pack,[33] and Sanders and Griffin[34] have advised that simple mastectomy be carried out on the opposite breast at the time of radical mastectomy.

Incision and excision of skin. A multitude of skin incisions have been proposed. Some present certain advantages but no one incision is ideal in every case. It is essential that the skin incision be individualized.

Controversy continues to rage regarding the amount of skin that should be removed at the time of radical mastectomy. Halsted[35] clearly stated that a large area of skin should be excised and the area grafted. He considered it hazardous to attempt plastic closure of the wound. Lewis and Rienhoff[20] have strongly seconded this concept. More recently, Haagensen[36] has advised a meticulous dermal dissection of the skin flaps in addition to skin grafting. On the other hand, ardent followers of W. S. Handley[37] have advocated extensive removal of fascia with primary plastic closure of the wound.

This controversy centers around the question of local recurrence. Those who advocate wide resection of skin and skin grafting are of the opinion that local recurrence is the surgeon's responsibility and can be prevented by wide removal of skin. However, Warren and Tompkins,[38] White,[39] and Conway and Neumann[40] have shown conclusively that the incidence of local recurrence in the skin is considerably higher in cases with involved axillary nodes than in cases without axillary involvement. In a review of 26 cases of local recurrence after radical mastectomy, Oliver and Sugarbaker[41] found that most of the patients had advanced disease at the time of operation and many could be classified as having categorically inoperable carcinoma. The conclusion seems justified that local recurrence is usually only another manifestation of the presence of widespread metastasis. No matter how radical the original operation may be, disease of this type cannot be expected to be accessible to the surgeon in most instances.

In table 2 [23,42,43] incidence of local recurrence after wide removal of the skin and skin grafting is compared with that after plastic closure. Since no significant difference is noticeable between the two methods of closure, skin grafting does not seem necessary as a routine measure.

TABLE 2
LOCAL RECURRENCE IN SKIN FOLLOWING RADICAL MASTECTOMY

Hospital	*Procedure*	*Local recurrence, per cent*
Presbyterian, New York [23]	Plastic closure	9.8
	Skin graft	15.3
Henry Ford, Detroit [42]	Plastic closure	5.5
	Skin graft	8.3
Massachusetts General, Boston [43]	Plastic closure and skin graft*	11.0

*Skin grafting not used routinely.

Some adjuncts to the surgical treatment of carcinoma of the breast have been developed since Halsted's original proposal. These include roentgen therapy, a wider knowledge concerning the role of the endocrine glands in health and disease, and the development of endocrine therapy.

Roentgen therapy. When carcinoma of the breast is treated by irradiation alone, 21 to 25 per cent of the patients will survive five years,[44] a figure comparable to that reported for untreated carcinoma of the breast.[45]

The preoperative use of roentgen therapy has with few exceptions[46] been abandoned. Adair[47] studied specimens removed by radical mastectomy in 119 patients given preoperative roentgen therapy and found viable cancer cells in 92 per cent of those with clinically involved axillary nodes. Furthermore, he has presented statistics showing a lower five-year survival rate for patients treated preoperatively with roentgen rays than for those treated initially by radical mastectomy.[22]

Enthusiasm for the use of postoperative roentgen therapy is more widespread although the demonstrable advantages are somewhat inconclusive on a statistical basis. Harrington's[48] figures show an 8 per cent improvement in the five-year survival rates of patients with involved axillary nodes treated postoperatively with roentgen rays. The number of patients not so treated was small so that statistically significant conclusions are not justified. Haagensen and Stout[23] have abandoned postoperative roentgen therapy in most cases because no advantage could be demonstrated from its use. A similar lack of benefit from postoperative roentgen therapy has been noted at the Johns Hopkins Hospital although postoperative roentgen therapy has been continued at that institution for patients with involved axillary nodes.[49]

In view of recent studies demonstrating a high incidence of involved supraclavicular and internal mammary nodes in patients with positive axillary nodes, it seems reasonable to irradiate these regions postoperatively in such patients in spite of the equivocal benefits reported. There is little question, however, that the use of irradiation therapy is of value in advanced and recurrent breast carcinoma to relieve suffering and achieve short-term prolongation of life.[23]

Oophorectomy. The use of irradiation to produce castration in cases of advanced carcinoma of the breast with metastasis deserves comment. The fact that estrogens may be an important factor in the growth and development of cancer of the breast has been appreciated for many years. Castration as a means of eliminating the chief source of estrogen would seem to be a logical procedure. However, prophylactic irradiation or surgical castration carried out at the time of radical mastectomy has not generally increased the rate of cure.[50] There is no doubt, however, that castration may be of material benefit, resulting in relief of symptoms, objective improvement, and prolongation of life in some premenopausal patients with advanced disease either primary or recurrent.[51] Because the degree of ovarian suppression obtained by irradiation is uncertain, particularly in young women, surgical oophorectomy is the procedure of choice.

Adrenalectomy. This means of eradicating another source of estrogenic substances has been advocated by Huggins and Dao[52] in the treatment of advanced carcinoma of the breast. When functioning ovarian tissue was present, they advocated bilateral adrenalectomy and oophorectomy.[53] Not all have been as impressed as they have been with the benefits of this procedure, but an occasional patient for whom all other methods of therapy have failed will obtain pronounced palliation after bilateral adrenalectomy.

Endocrine therapy.[54,55] The use of hormones as a palliative measure in advanced carcinoma of the breast is now generally accepted. In spite of the fact that estrogen is apparently necessary for the growth of some cancers of the breast, it has been shown to have an inhibitory effect as well. It is used primarily in patients with advanced disease, five years past the menopause, and has its greatest benefit in the palliative treatment of soft tissue metastasis although occasionally osseous metastasis may be affected. The optimal daily dose is 15 mg. of stilbestrol or its equivalent with other compounds. Objective regression of disease in 40 to 50 per cent of cases and subjective improvement in 60 to 80 per cent of cases may be expected.

Androgens are indicated as palliative agents in women with advanced disease regardless of age, particularly in the presence of pain and weakness secondary to osseous metastasis. Calcification of osteolytic lesions may be observed in 20 to 25 per cent of cases. Use of testosterone in doses of 150 to 300 mg. per week in divided doses has been advocated.

A recent report suggests that there are two types of mammary cancer, one dependent on estrogen for its growth and development and the other independent of estrogen. The former is benefited by surgical castration and adrenalectomy, the latter by the use of cortisone.[56]

All of these ancillary methods of treatment—castration, adrenalectomy, and hormone therapy—

should be reserved for the time when orthodox methods of treatment, namely, surgery and irradiation, cannot be applied or have proved unsuccessful.

Statistical data. The recently published figures on the results of radical mastectomy from major surgical centers of this country are summarized in table 3. In general, three-fourths of the patients without involvement of the axillary lymph nodes and only about a third of patients with involvement of axillary lymph nodes survive five years. More than half of all patients operated on survive five years. The over-all rate of cure is significant. These figures refer to the number of patients living without disease as a percentage of all patients seen during the stated period whether operated on or not and approach 40 per cent. Viewing these figures in relation to five-year survival in untreated cases (22 per cent) is cause for some discouragement. In fact, Park and Lees[57] have recently pointed out that it is extremely doubtful that the survival rate of cancer of the breast is influenced by treatment at all. Their conclusions are based on extensive statistical studies including some statistical maneuvers which will not be discussed except to say that their validity is questioned by other statisticians.[58,59]

It has been pointed out that along purely statistical lines there has been no fall in the death rate from carcinoma of the breast in the population as a whole.[10,60] McKinnon[60] claimed that the failure of early treatment to reduce mortality from cancer of the breast shows that remote metastasis occurs before interference is possible.

Evidence that treatment is of value in carcinoma of the breast is suggested by table 4. The five-year survival rates are given for patients operated on at the Mayo Clinic in successive five-year periods from 1910 through 1944. A definite and consistent increase in survival rates is evident in both cases with and without axillary node involvement. The figures for patients with involved axillary nodes are pertinent for in these cases there can be no question of the diagnosis being incorrect. Furthermore, results in recent years cannot be said to be better because the lesions are less malignant since all had metastasized to the axillary nodes when operation was carried out. Improvement in survival in this group must be due to improved and earlier treatment.

In any event, dissatisfaction with current methods of treatment have led investigators to search for possible reasons for the continued high death rate from carcinoma of the breast and possible alternate methods of treatment.

SUPERRADICAL OPERATIONS

Recent studies on the lymph drainage of the breast have prompted the suggestion that more radical removal of potentially involved lymph nodes may increase the survival rate.

The lymph drainage of the breast is directed primarily into two main depots, the axillary nodes and the internal mammary nodes. From these depots, secondary drainage occurs into the nodes at the base of the neck and into the venous system at the point at which the jugular and subclavian veins join. When the disease has reached the subclavicular node or the nodes in the first intercostal space, the sentinel node in the neck is also very apt to be involved or blood stream dissemination has occurred. Any further involve-

TABLE 3

RECENT RESULTS OF RADICAL MASTECTOMY FOR CARCINOMA OF THE BREAST

		Patients		*Five-year survival, per cent of cases*			
Name	*Year*	*Total*	*Operation on*	*No axillary nodes*	*Axillary nodes involved*	*Total*	*Over-all five-year cure*
Adair [22] Memorial Hospital, New York City, 1935-1942	1949	3,355	1,913°	78.6	42.2	56.2	39.6†
Taylor [43] Massachusetts General Hospital, Boston, 1936-1941	1950		430 (80%)	79†	41†	56†	
Haagensen & Stout [23] Presbyterian Hospital, New York City, 1935-1942	1951	668	495 (74%)	71†	34.8†	58.2	38.6†
Harrington‡ [48] Mayo Clinic, Rochester, Minnesota, 1910-1944	1952		7,325	78.3	32.5	51.2	
Lewison [49] Johns Hopkins Hospital, Baltimore, 1935-1940	1953	255	204 (80%)	64.1	31.7	44.1	38.2†

°Operability cannot be accurately stated. Many patients with operable lesions received x-ray therapy.
†5-year cure rates. Patients living with recurrent disease excluded.
‡Untraced patients not included in statistics.

TABLE 4
FIVE-YEAR SURVIVAL RATES AFTER RADICAL MASTECTOMY DURING DIFFERENT FIVE-YEAR PERIODS*

Period of operation	WITH METASTASIS			WITHOUT METASTASIS			TOTAL		
	Number traced	Number	Per cent†	Number traced	Number	Per cent†	Number traced	Number	Per cent†
1910-1914	303	71	23.4	214	134	62.6	517	205	39.7
1915-1919	592	155	26.2	294	210	71.4	886	365	41.2
1920-1924	659	156	23.7	360	252	70.0	1,019	408	40.0
1925-1929	762	248	32.5	399	308	77.2	1,161	556	47.9
1930-1934	612	216	35.3	403	329	81.6	1,015	545	53.7
1935-1939	662	268	40.5	589	482	81.8	1,251	750	60.0
1940-1944	741	292	39.4	735	629	85.6	1,476	921	62.4
Total	4,331	1,406	32.5	2,994	2,344	78.3	7,325	3,750	51.2

*Reprinted with permission from Harrington, S. W.: Results of Surgical Treatment of Unilateral Carcinoma of Breast in Women. J.A.M.A. 148:1007-1011, 1952.
†Based on patients traced by inquiry as of January 1, 1950.

ment of supraclavicular lymph nodes is by retrograde extension.[27]

Stibbe[61] at the suggestion of W. S. Handley studied the anatomy of the internal mammary lymph nodes. He found these nodes more frequently and in larger numbers in the first, second, and third intercostal spaces lying in the fatty areolar tissue on the endothoracic fascia in the plane of, or superficial to, the plane of the internal mammary artery and veins. Soerensen[62] and Ju and associates[63] noted a more even distribution of the nodes with a gradual diminution in the concentration in the lower interspaces.

Recent pathologic studies[1,5,7,64–66] have indicated that the regions of the supraclavicular and internal mammary lymph nodes are involved far more frequently in so-called operable carcinoma of the breast than was hitherto appreciated (table 5). These studies show that these regions are involved more frequently when the axillary nodes are involved than when they are not. Involvement of the internal mammary lymph nodes is more frequent when the primary lesion is in the central or medial portion of the breast than when it is in the outer portion.

The concept of a more radical surgical attack to encompass lymph nodes beyond the scope of the classical radical mastectomy is not new. Halsted himself carried out supraclavicular dissections in patients with carcinoma of the breast. By 1907 he reported having carried out such a procedure in 119 cases. The nodes were involved in a third of the patients and only 2 lived five years.[35] In 1898 he wrote, "Dr. H. W. Cushing, my house surgeon, has in three instances cleaned out the anterior mediastinum on one side for recurrent cancer."[67]

Andreassen and Dahl-Iversen[1] have recently combined dissection of supraclavicular lymph nodes with radical mastectomy in 98 patients. Gardner and associates[3] have combined dissection of the supraclavicular and internal mammary chains in a small group of patients. Recently at the University of Minnesota hospitals, 50 patients with carcinoma of the breast have had radical mastectomy and, either at the same stage or at a second stage, supraclavicular dissection with internal mammary and anterior mediastinal dissection. The mortality rate was 13 per cent.[7]

Gordon-Taylor[68] has stated that in more than a dozen cases he has removed the chain of anterior mediastinal lymph nodes along with the internal mammary vessels after resection of the second and third costal cartilages. Margottini[6] has performed a similar procedure on 227 patients. In this country, Urban[5] has advocated radical mastectomy in continuity with en bloc resection of the internal mammary chain of lymph nodes, primarily for centrally or medially located lesions. By July 1952, 57 such patients had been operated on; only 1 death occurred.

Whether or not these radical procedures will increase the survival rate for patients with carcinoma of the breast remains to be seen. Sufficient time has not yet elapsed for proper evalua-

TABLE 5
INVOLVEMENT OF LYMPH NODES IN OPERABLE CARCINOMA OF THE BREAST

	LATERAL LESIONS	MEDIAL LESIONS	TOTAL	AXILLARY NODES INVOLVED
	Internal mammary nodes involved, per cent of cases			
Dahl-Iversen[61]	12	30	19	24
Handley[65]	18	54	33	44
Hutchinson[66]	28	20	26	46
McDonald*[27]	21	41	34	
Urban†[5]		49		73
Lewis[7]	In 60 per cent of cases supraclavicular, or mediastinal nodes or both are involved when axillary nodes are involved.			
	Supraclavicular nodes involved, per cent of cases			
Andreassen[1]			17	33

*Only patients with clinically involved axillary nodes or central and medial lesions were studied.
†Primarily central and medial lesions.

tion. A procedure such as Wangensteen's which is accompanied by a mortality rate of 13 per cent seems unjustified. Furthermore, as McDonald and his associates[27] have pointed out, if the disease has not reached the lymphatic terminus at the junction of subclavian and jugular veins, Wangensteen's operation is too radical. If the disease has reached this point, probably blood stream dissemination has already occurred.

It is possible that some patients, particularly those with centrally or medially located lesions, will be benefited by dissection of the internal mammary lymph nodes. Before such a procedure is carried out, preliminary biopsy of the supraclavicular region and the first intercostal space should be done, for as was pointed out previously, if nodes in either of these areas are involved, chances for surgical cure are remote.

SIMPLE MASTECTOMY AND ROENTGEN THERAPY

A controversial method of therapy has been reintroduced by McWhirter of Scotland, namely, simple mastectomy and irradiation.[8–13] The decision to study such a method of treatment was reached by McWhirter and his surgical colleagues in 1941 after review had proved that the results of radical mastectomy were disappointing. The rationale behind their decision is:

1. Radical mastectomy is a failure in 75 per cent of cases. This conclusion is based on the assumption that with an operability rate of 56 per cent and a five-year survival rate of 45 per cent, the over-all five-year survival rate is only 25 per cent. Their experience in Edinburgh prior to 1941 was comparable to this.

2. Simple mastectomy is adequate when the disease is localized to the breast. If the axilla is involved, radical mastectomy gives poor results and there is danger of spreading disease through newly opened channels.

3. In most cases of carcinoma of the breast, radical mastectomy is apt to be ineffective unless accompanied by roentgen therapy. Roentgen therapy is successful in reducing local recurrences so that it must destroy cancer cells and can be used to treat the axilla.

4. A larger percentage of the total number of patients seen can be treated by such a regimen than with radical mastectomy, including patients with fixed axillary nodes and enlarged supraclavicular nodes.

5. Delay in starting roentgen treatment is less when simple mastectomy is employed and consequently the time during which metastasis can occur is less.

6. Postoperative morbidity in the form of lymphedema is negligible with simple mastectomy and roentgen therapy.

Special technics are employed in carrying out this program. The skin is carefully treated, and no iodine or adhesive is used. A short incision is used and wide dissection is not carried out. Roentgen therapy is started after two weeks and a minimal dose of 3,750 r is given; 4 fields are used.

McWhirter has emphasized correctly the importance of including all cases of cancer of the breast seen in arriving at survival statistics, and he has conscientiously done this in his reports. His statistics for similar periods supposedly on the same group of cases, however, vary from one report to another. Thus, in one report the operability of cases seen from 1935 to 1940 is 56 per cent[10] and in another it is 65 per cent.[12] The reports of five-year survivals differ similarly. Furthermore, the figure he used most often as the five-year survival rate of all patients seen from 1941 through 1945 when simple mastectomy and roentgen therapy were used, namely, 43.7 per cent, was published in 1948 before all patients could have been followed five years. This figure has apparently not been revised subsequently. Finally, certain unexplained deductions are made in his statistics for patients dying of intercurrent disease. Nevertheless, the over-all results are certainly admirable and are comparable to the results obtained in surgical centers in this country where radical mastectomy is the treatment of choice (table 6).

Some controversial points should be raised in regard to the rationale of such treatment. In the first place, as suggested above, the results of radical mastectomy as carried out in this country are not as bad as claimed. The poor results obtained in McWhirter's early series were accompanied by a 38.7 per cent incidence of local recurrence.[8] The obvious conclusion is that many of these lesions were inoperable and it is well established that radical mastectomy in such advanced cases actually shortens life.[23] The operability rate in this country ranges from 74 to 80 per cent[23,43,49] instead of 56 per cent which McWhirter claimed.[10] In fact, in one of McWhirter's own reports the operability rate was 65 per cent.[12] In a discussion of one of his own papers McWhirter gave five-year survival rates for radical mastectomy of 80.5 per cent for patients without involvement of axillary nodes and 45.4 per cent for patients with involved axillary nodes.[69] It is hard to see how he could be dissatisfied with radical mastectomy with such excellent figures available.

His argument that simple mastectomy plus

TABLE 6
COMPARISON OF RESULTS OF VARIOUS FORMS OF TREATMENT FOR CARCINOMA OF THE BREAST

Author	Years	Method of treatment	FIVE-YEAR SURVIVAL, PER CENT OF CASES: For operable lesions	Overall
McWhirter	1930-1934 [8]	Radical mastectomy	35.6	
	°1935-1940[10]	Radical mastectomy and roentgen therapy	50.1	32.4
	°1941-1945[10]	Simple mastectomy and roentgen therapy	62.1	43.7
Haagensen [23]	1935-1942	Radical mastectomy (plus roentgen therapy in 1/3)	58.2	47.2
Lewison [19]	1935-1940	Radical mastectomy (plus roentgen therapy for involved axillary nodes)	44.1	43.2
Harrington [48]	1940-1944	Radical mastectomy (plus roentgen therapy for involved axillary nodes)	62.4	

°Highest survival figures are given here. Other reports give lower five-year survival rates.[8,9,12]

roentgen therapy is a treatment which is available to a greater percentage of all patients seen is questionable. Unfortunately, he gives no figures on the percentage of patients he actually treats in this way. He does say, however, that only a limited number of patients with inoperable lesions can be treated by simple mastectomy and roentgen therapy.[10] Any increase in survival statistics in this group, therefore, must be due primarily to roentgen therapy and would be applicable in institutions preferring radical mastectomy for operable lesions provided McWhirter's technics were used.

McWhirter's assumption, that roentgen rays actually destroy cancer cells in the axilla, can be seriously questioned. Previous studies on this point have been mentioned. McWhirter himself said that his patients may have viable cancer cells in the axilla.[69] Whether the restraining effects of radiation will last indefinitely is uncertain. To answer this question ten-year survival statistics must be available.

McWhirter's claim that roentgen therapy can be started earlier when simple mastectomy is performed than when radical mastectomy is carried out is a doubtful one. In most cases roentgen therapy may be started on the tenth to the fourteenth day after radical mastectomy.

According to McWhirter, lymphedema of the arm seldom occurs with his method of treatment and morbidity is negligible. With radical mastectomy, significant degrees of lymphedema should not occur in more than 7 per cent of cases.[70] Using a modified version of McWhirter's technic, Gilmore[71] reported the following incidence of complications: uncomfortable edema of the arm in half of the patients treated; pulmonary fibrosis in a third; some degree of irradiation necrosis of the surgical scar in a fourth; and occasional pathologic fractures of ribs from necrosis.

Final acceptance or rejection of McWhirter's proposal must await a longer period of evaluation. For the present, most large medical centers in this country are continuing to treat operable carcinoma by radical mastectomy.

SUMMARY

Since its introduction 60 years ago, radical mastectomy has constituted the best surgical procedure available for the treatment of carcinoma of the breast. Today this procedure can be expected to result in the five-year survival of more than three quarters of the patients without involvement of axillary nodes and of a third of the patients with involvement of axillary nodes. More than half of all patients so treated may be expected to live five years.

Recent pathologic studies have indicated a high incidence of involvement of supraclavicular and internal mammary nodes in cases of operable carcinoma of the breast. More extensive operations have been devised to encompass more of lymph drainage of the breast. Simple mastectomy with roentgen therapy has been proposed as the procedure of choice for carcinoma of the breast.

Although both of these procedures may find their proper place in the therapeutic approach to the problem of carcinoma of the breast, sufficient time has not elapsed for proper evaluation of either method.

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Treatment of Migraine in College Students*

KENNETH R. MAGEE, M.D.
Ann Arbor, Michigan

As the University of Michigan Student Health Service employs a consultant neurologist, a unique opportunity is given to study various neurologic disorders common to the college age group. By far the most frequently observed complaint is that of headache. Although tensional or psychogenic factors are responsible for the majority of these headaches, a large number of students with migraine are encountered. The proper treatment of this disorder is very important for the completion of a successful college career. Though, in essence, the treatment is similar to that of an adult, a sufficient number of different factors pertain to the college group to present results of treatment and introduce certain concepts regarding the proper handling of migraine in their particular instances.

Very little need be said regarding diagnosis. The classical finding and variants usually encountered in migraine and the differential diagnosis from other headaches have been reviewed frequently by DeJong,[1] Friedman,[2] Wolff,[3] and others and need not be repeated. However, the physician must be alert, as the common history of repeated episodes of hemicranial pain involving either side, usually associated with nausea and vomiting, are often absent. This is due to the fact that the first attack of migraine often occurs at college age, resulting in the prompt visit of an alarmed patient to the doctor, wondering what strange disorder has befallen him. Diagnosis should be made at this time and the details discussed with the patient, reassuring him that no serious organic disorder, particularly a brain tumor, has been found. An effective program of treatment can then be outlined, saving him much further mental and physical anxiety.

PRINCIPLES OF TREATMENT

Psychologic factors are of paramount importance and are the most difficult to treat. The tension and strain of a busy college career often seem to "trigger" the migraine attack, and the students confronted with such a situation have the most frequent headaches. These young people are coming face to face with a new experience—an intensive competitive college program in which they no longer find themselves in the superior position that most of them knew in high school. Many are homesick, tense, anxious, and afraid. Thus it is little wonder that symptoms are prone to develop at this time. These students are not simple to help, but all possible aid should promptly be given. A thorough discussion of their feelings regarding college and constructive efforts in the direction of more adequate insight and adaptation is often rewarded by increased efficacy of treatment. Unfortunately, simple measures may not be sufficient and occasionally more deep-seated personality disorders are present which require technical and more extensive approaches in management. Frequently the reaction precipitating the headache is realistic. A patient who notes exacerbations of his migraine coinciding with increased work prior to examinations is not easily reassured when informed that increased tension and anxiety aggravate his migraine. He is apt to inquire what he can do when faced with examinations. If he becomes more relaxed and his grades become poorer, he finds himself in a greater state of tension than before, and consequently his migraine does not improve. This problem defies simple affirmation because obviously a few well chosen words per se cannot remake a tense, driving individual, as the migraine sufferer often is, into a calm and relaxed student. The most satisfactory solution to this type of reaction rests in proper counseling at the beginning of the semester in finding a suitable program of courses that can be readily handled without overwork. A reduced load may be the solution, but this is better than the vicious cycle that results from excess work with subsequent headache, poorer grades, tension, and anxiety.

Kenneth R. Magee, *a 1948 graduate of the University of Chicago School of Medicine, is clinical associate at the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.*

*From the Department of Neurology and Mental Hygiene Unit of the Student Health Service, University of Michigan, Ann Arbor.

There are two other specific fears tending to promote the patient's anxiety and his headaches that should be met and dealt with promptly. The first is the fear of a brain tumor. In the more "informed" college populace, this fear is often great and is present in the majority of patients. The onset of this one-sided headache with nausea and vomiting is new and alarming to these young people and it is wise categorically to tell every patient with migraine that he does not have a brain tumor. Often the student who has not expressed this fear looks relieved and admits that he did fear a brain tumor, but was afraid to express this fear.

The other fear disturbing the patient's peace of mind is that of missing an examination or of doing poorly because of a headache. I find it wise to tell each student initially that if he does poorly in an examination to report that the poor performance was the result of a migraine attack, and that I will be glad to explain matters to the instructor. The student seldom takes advantage of this offer, but the fear is dispelled that he will have to tell the instructor that he did poorly or missed an examination because of the non-obvious and unsatisfactory excuse of a "headache."

Although the previously mentioned methods of promoting the patient's mental health often are not enough to stop the migraine attacks, in many cases the frequency is significantly lessened and drug therapy can be used to better advantage. At this early age, other things being equal, direct simpler measures along mental health lines as opposed to formalized psychotherapeutic approaches, together with an appropriate medical regime can do much to help students adjust, not only through college but through the rest of their careers, to these inevitable periodic headaches with actual reduction in frequency and severity. The pattern of reaction to the disorder that is established at this time may persist through life. Therefore, the importance of management at this early period should not be minimized.

Drug therapy is extremely important in treating migraine, as excellent results can often be obtained with appropriate medications. There are two methods of approach to drug treatment. The first consists in treatment of each individual hemicranial attack. The second approach attempts to reduce the frequency of the attacks. To treat the individual headache, ergotamine tartrate is the specific drug of choice. Available in 1-mg. tablets alone or combined with 100 mg. of caffeine (Cafergot), 1 to 3 or 4 tablets should be prescribed at the onset of each attack. The importance of taking the medication the moment the patient can tell that a headache is beginning should be stressed. After the headache is established, the effect of ergotamine is not nearly so efficient. Cafergot, containing ergotamine tartrate and caffeine, is considered by some investigators to be more efficient than ergotamine alone, but with care in instructing the patient in the use of the drug, we have found little difference between the two. Ergotamine tartrate (Gynergen) can be given hypodermically in ½- to 1-cc. doses, but this is often impractical as the patient rarely receives the injection at the most effective time — the very onset of the headache.

A third method of administering ergotamine is by suppository.[4] In our experience, many patients who fail to benefit from oral preparations respond excellently when ½ to 1 suppository containing 2 mg. of ergotamine tartrate and 100 mg. of caffeine is prescribed. The practical difficulty with this method of administration is due to the frequent inability of the student to use the suppository at the beginning of the headache. Despite this objection, however, the rectal use of Cafergot promises to aid many people who were refractory to the oral compound.

Though constructive psychological approach is sine qua non and should always be borne in mind, certain medications occasionally help reduce the frequency of the patient's attacks. Small doses of phenobarbital, ergotamine tartrate, and belladonna (Bellergal), given three times daily appear to reduce the frequency of the headaches. Unfortunately, however, many students note no effect from these drugs.

RESULTS

The series consisted of 115 patients who received treatment for migraine. Of these, 71 were male and 44 female. The average age of the group was 21 for the women and 23.2 for the men. The average age of onset of the migraine was 20.3 for men, 18.4 for women. A history suggesting that "sick headache" was present in 1 or more relatives was given by 43 patients or 37 per cent. The results of treatment are shown in table 1. Results are listed as "excellent" if the patient experienced complete relief from headache within two hours, "good" if relief was substantial but not complete within four hours, and "poor" in patients who found little or no benefit, or in whom side effects precluded the use of the drug.

Routine analgesics, though rarely given as a procedure of choice, had been used at one time or another by most of the students. These con-

TABLE 1

	Total	Excellent No.	%	Good No.	%	Poor No.	%
Oral ergotamine	85	32	38	30	35	23	27
Ergotamine-caffeine suppositories	29	13	45	8	27.5	8	27.5
Mild analgesics	94			8	8	86	92

sist of aspirin or phenacetin with or without small amounts of codeine.

The failure of simple analgesics to relieve the pain is to be expected, but should the patient have found relief by such simple measures, he might not have consulted the neurologist.

Continued use of narcotics, even codeine, is, of course, inadvisable because the recurrent nature of the affliction necessitates frequent medication with danger of addiction.

The results are not as satisfactory as other published series on the treatment of migraine with ergotamine compounds, but do indicate that a large percentage of patients can be materially benefited by following the principles previously outlined. Aside from medical treatment, 25 students from this series were followed by a psychologist, social worker, or psychiatrist.

Through the years, migraine has often been said to be found in tense, hard-working, driving, ambitious people. The suggestion has been made occasionally that the person afflicted with migraine may be more intelligent than average. Though elaborate statistical analysis could not be made, the average grades for a group of about 2,000 university students prepared for selective service purposes were obtained and showed an approximate average of 2.60 where a grade of B is equivalent to 3, and C to 2. The average is seen to be about C+. In a series of 50 comparable students with migraine whose averages could be obtained, the grade point average was 2.64. Thus the difference between the 2 groups is not pronounced, though, of course, college grades are not indexes of intelligence.

SUMMARY

The importance of prompt and efficient medical and psychologic treatment of migraine in the college student is stressed. Methods of treatment with results in 115 cases of migraine are analyzed. A limited comparison of scholastic standing of students indicates no significant difference from other students.

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Local application of a 2.5 per cent suspension of hydrocortisone acetate in nasal jelly is especially useful for less reactive forms of nasal allergies. When specific hyposensitization is undertaken simultaneously, Thomas Timothy Smith, M.D., of Omaha finds that the effect of medication is enhanced. The hormone is of little value when injected into the submucosa of the turbinates or instilled into the sinuses for the relief of maxillary sinusitis. The addition of 5 per cent pyrilamine maleate to the jelly appears to diminish the effectiveness.

Thomas Timothy Smith: Arch. Otolaryng. 60:24-35, 1954.

Lancet Editorial

DR. ARTHUR K. SAIKI - An Appreciation

■ Dr. Arthur K. Saiki, professor of pathology at the University of North Dakota and state pathologist, has just completed his twenty-fifth year of service to the University medical school. He was guest of honor at the December Grand Forks District Medical Society meeting and tribute has been paid him by his associates and medical school alumni. A portrait of Dr. Saiki is to hang in the new University medical school, now under construction on the campus in Grand Forks.

Dr. Saiki was born in Hawaii, July 29, 1900, and attended grade school and high school there. After receiving his B.A. degree from the University of Hawaii, he entered medical school at the University of North Dakota at Grand Forks. Upon completion of two years of study, he transferred to the University of Nebraska College of Medicine at Omaha where he received his medical degree in 1928.

Dr. Saiki did postgraduate work at the University of Michigan School of Medicine, Pennsylvania Medical College, Columbia University College of Physicians and Surgeons, Rush Medical College, and Harvard University. He holds membership in the North Dakota Academy of Science, Sigma Xi, the American Association for the Advancement of Science, and the American Association of Medical Museums. He is a diplomate of the American Board of Pathology and a fellow of the College of American Pathologists. He has been a contributor to several medical journals and is listed in *Who's Who in the Midwest* and *Who's Who in America.*

Dr. Saiki's long years of service to the University of North Dakota began after graduation from the University of Nebraska when he became instructor of physiology and pharmacology. In 1930 he was appointed assistant professor of pathology and bacteriology, a position he held until 1936. Until 1949 he served as professor of pathology and bacteriology when he became professor of pathology, the position he holds at the present time.

Dr. Saiki married Lydia E. Kuoppala, of Plummer, Minnesota, who died in 1938. His two sons, George and John, are attending school in Grand Forks and both boys are planning medical careers.

The last letter in our series of Notes from a Medical Journey from Dr. Ancel Keys, head of the department of physiological hygiene at the University of Minnesota, to Dr. J. A. Myers and the readers of THE JOURNAL-LANCET *was published in July. Dr. Keys returned to the United States for the summer, but is now again in Italy doing further research on cholesterol metabolism and its relationship to nutrition and cardiovascular disease. We are delighted to have the opportunity to present another letter—the first we have received since Dr. Keys returned to Italy in October.*

Notes from a Medical Journey

October 21, 1954
Bologna, Italy

Dear Jay:

On Friday in New York there were headlines, "Hazel here at 5 p.m." but that is flight time and hurricanes were not on my agenda. No matter, bend over and push hard walking out to the airplane. Too bad about the lady's hat skittering by in the 50-mile wind. The Constellation needs none of the usual long run before we are flying into the air, leaving behind me what little enthusiasm I have about flying anyway. But in half an hour all is smooth, engines roaring monotonously as we cut a damp tunnel through endless clouds. Strictly routine; it is raining in Shannon -- it always rains in Shannon -- and then holes in the clouds and we are out in the sun over France.

The 'plane cabin gets hot as we wait to take off from Paris. Why the delay? Oh! the young man with the little beard is an Arab prince and the difficulty is where to put all his luggage. A thousand dollars for surplus baggage and he has a retinue of 20, all men. The Arab ladies stay home. I wonder, does he have a harem? Why bring them to Paris? Coals to Newcastle. That is Lake Geneva sparkling below us and the snow on Mont Blanc is pink in the late afternoon sun. Now it is dark again and those sparse lights so far below are little Italian villages. Buona sera! Que piacevole! Can I remember Italian?

We are two hours late at Rome but there are Flaminio Fidanza and his brother, waving under the floodlights on the airport terrace, and then we are dashing along the Appian Way in the little Fiat. No, it is not too late for a proper dinner, and, yes, first leave the bags at the hotel, and Doctor Fidanza Senior is very well and I agree that Swahn's lipoprotein method is not very reliable, OK to use the Bismarck Black stain to find the boundary between the alpha and beta fractions. There is no doubt that vegetable fats in the diet influence the serum cholesterol level but perhaps animal fats have more effect. We must study a population on a high vegetable fat diet. Some place in Puglia, down at the heel of Italy or, better still, the Island of Crete. Too bad they speak Greek

there, but for dinner they have a loaf of bread and a bowl of olive oil. Dip the one in the other, and the Rockefeller Survey got some mortality data on Crete but no mortality rates specific for age and cause. Must get someone to do a clinical survey on Crete; Dr. Paul White knows some Greek cardiologists, but all this will take time in planning.

In the meantime, why not work in Sardinia next April? The diet is even less fat than in Naples and the vital statistics indicate very little heart disease. Dr. Sotgiu, professor of medicine at Bologna, is from Sardinia and Drs. Poppi and Postelli of Bologna are also keen about Sardinia. We could make a better test of ballisto and electrocardiographic age trends. Compare men of Minnesota with men of Sardinia, better than Naples, and we can get more help. How much cholesterol in the beta lipoprotein fraction? That will have more meaning for atherogenesis than cholesterol or any amount of ultracentrifuging and the beauty of it is that we can run the paper electrophoresis easily in the field and do the chemical work on the paper samples months later. Our new micro cholesterol method will handle it beautifully.

And so it is Monday. In between there was exhausted sleep and miles and miles of walk and talk, over all the hills of Rome. Professor Kimura's analysis of 10,000 autopsies in Japan really shows the great rarity of coronary disease there and the diet provides only 8 per cent of the calories from fats and Flaminio is much impressed, as I expected, but there is no good place to sit down on the Palatine. The Janiculum will be better so across the Tiber to Trastevere -- how compact and expressive Italian place names can be! Stop for lunch, table out of doors but under an awning for it is warm. Start with mussels gratine and finish with pears and fresh, sweet Parmesan cheese. Up, up the hill of Janiculum, gardens filled with cypress and junipers trained and pruned to represent all sorts of animals and figures and then to the parapet, a little sweaty and short of breath, to gaze down on the Tiber and across to all of Rome, while we agree that the Italian medical schools can never really reach the first rank until they pay enough to keep full-time professors, and somehow reduce the autocratic authority of the department heads. It is the same in France and worse in Spain. To suggest the Socratic method of teaching here would create a scandal.

All day Monday, at the FAO headquarters of United Nations, is spent in drafting "working papers" for the coming Joint Experts' Committee Meeting at the headquarters of WHO at Geneva. It is a pity to deny the tempting day outside, a golden glow on all of ancient Rome spread out below the window. But my 1951 plea for attention to the influence of nutrition on "degenerative" disease now has a spot on the agenda and I must marshal the facts in concise argument.

Why should WHO and FAO give all attention to problems in "underdeveloped" countries? What are the real health problems of the U.S.A., Britain, Scandinavia, and so on? Why is there so little coronary disease in Japan and among all peoples who work hard and shun rich, fatty food? They would probably eat it, all right, if they had it, and then they would

fall heir to our troubles. How long would it take? When the war forced fats from the tables of Europe, less than two years sufficed to bring adult mortality rates tumbling down, the postmortems showing much less atheroma. And then the glorious victory, a world to be rebuilt, back to good living, and the mortality graph switches up again. Now we shall progress, more and more is better and better; more sugar in the blood, more fat in the liver, more cholesterol in the blood, more blubber on the belly. Quick, we need more insulin, more oxygen, more hospital beds, more young widows. Los Angeles has more automobiles than anybody and who cares about the smog? You can't have prosperity without a little flatus.

Italy, also, is more prosperous. Too bad there is quite a lot of unemployment; too bad they don't send Togliatti back to Russia where he belongs; too bad there are so many Italians and no oil or coal or iron in rocky, beautiful old Italy. But the birth rate in Italy is less than in the States and besides Togliatti and his hard core of a hundred thousand real communists, there are millions of Italians who say, "Well, what do we do? We work hard, we are patient and cheerful and clever; we can make anything. You should see our new buildings and our old ones, look at our autos and roads and see what a good diet and good eating we can concoct from the cheapest of foods, and listen to us sing and laugh all the time. But what do we do to make a better life for all of us? Give me a job and give me some tools to work with. If I can only carry things like a donkey, then I can't get more than a donkey's wages." There are millions like this and to go stamping around talking about H-bombs doesn't help.

And here I am in Bologna, seeing about skinfold calipers and plans for research and being stuffed with the rich food of Bologna by my good friends who don't seem to worry about the intimal deposits in my coronary arteries. Tomorrow I shall escape to Rome for the week-end before going on to Geneva. But much has been accomplished and the arrangements for Sardinia are well in hand. Our clinical friends are enthusiastic about a big survey of the kinds of illness in Sardinia and here in Bologna. Two very different diets and we shall see what happens in April.

With all good wishes to all in Minnesota.

As ever,

Ancel Keys

Lancet CLINICAL REVIEWS

This department of THE JOURNAL-LANCET *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Shigellosis in Six Siblings

WILMER L. PEW, M.D.
Minneapolis, Minnesota

BACILLARY dysentery is an acute infectious disease caused by various strains of Shigella. The acute phase of the disease is characterized by abdominal pain and frequent stools which may contain blood, pus, or mucus. A disease of the tropics, dysentery is unusual in temperate areas. At Minneapolis General Hospital only about a dozen stool cultures are found positive for Shigella each year. Most of these patients do not have an acute infection.

Dysentery is usually spread by food or water contamination. Although the disease occurs among all age groups, adult males between 20 and 30 years of age and children under 2 years of age are afflicted most frequently. A single attack may immunize the patient against that particular strain, but recurrences are common. The pathology consists primarily of involvement of the lymphoid follicles of the colon and the production of shallow, serpiginous ulcers in the mucous membrane of the colon.

The incubation period varies from one to seven days. The disease takes many forms varying from mild diarrhea to acute, fulminating forms. The usual case starts acutely and may be accompanied by copious diarrhea, tenesmus, fever, headache, vomiting, and drowsiness. Occasionally meningism is seen. Rapid dehydration may occur in children.

The common complications are nonsuppurative arthritis and anemia. Stenosis of the colon is seen in the chronic forms.

The diagnosis may be suspected by the clinical picture but must be verified bacteriologically using specific culture media. An anoscope may be used for swabbing the rectal mucosa directly. Hardy and Watt[2] have described a method for large scale culturing using a simple swab in a rubber tube.

The prognosis varies, fatality rates of 5 to 10 per cent have occurred in severe outbreaks.

WILMER L. PEW, *a specialist in pediatrics, is with the department of pediatrics at the University of Minnesota hospitals.*

The treatment consists of bed rest, adequate hydration, sulfadiazine and the broad spectrum antibiotics. Sulfadiazine is administered to children in doses of 1 to 2 gr. per pound of body weight per day. The tetracycline drugs are administered in doses of 20 mg. per kg. every twenty-four hours in divided doses orally. Polymyxin has been advanced as a useful drug, but some hesitation exists due to reported severe side effects. The drug is effective orally. Normal diet should be resumed gradually. Fluids should be given at first and then low residue foods. The patient should be isolated until 2 negative stool cultures have been obtained at a twenty-four hour interval.

Following is a report of an experience with this disease. On October 6, 1952, 5 siblings ranging in age from 4 months to 9 years were admitted to the Minneapolis General Hospital with complaints of vomiting and diarrhea of eighteen hours duration. The positive findings on admission are summarized in table 1.

The sixth child, a 7½-year-old girl, had developed similar symptoms on October 2, 1952. The following day she became comatose and was admitted to a hospital in Colorado where, despite vigorous therapy, she expired on October 4. The parents were returning to Minneapolis for the funeral when the other children became ill. No history of similar illness could be traced to the parents or associates of these children.

L. F., a 6-year-old boy, was critically ill, very dehydrated, lethargic, and at times almost unresponsive. All the children exhibited some degree of dehydration but no other striking physical findings. In view of the history, all were treated as acute emergencies. Blood cultures and chemistries were drawn, and the rectal mucosa was carefully swabbed through an anoscope and plated directly on Salmonella Shigella agar plates. The children were given nothing by mouth. Hydrating solution consisting of ⅓ normal saline and ⅔ 5 per cent glucose in dis-

TABLE 1

	Age	Temperature	Vomiting: History	Vomiting: Hospital	Diarrhea: History	Diarrhea: Hospital	Dehydration	Other
J. F.	4 mo.	98.6	3+	0	0	0	1+	None
D. F.	2 yr.	98	2+	0	2+	4+	2+	Sl. pharyngitis
S. F.	4 yr.	102.4	2+	0	2+	4+	3+	Sl. pharyngitis
L. F.	6 yr.	104.6	3+	1+	4+	4+ bloody	4+	Lethargic Sl. pharyngitis Postnasal drip Sluggish reflexes Meningismus, minimal
D. F.	9 yr.	97.8	2+	0	2+	1+	1+	Sl. pharyngitis

TABLE 2

	Age	Serology	Hemoglobin	WBC	Differential	Urine	BUN	CO_2	Cl	Ca	Albumin	Globulin	Bilirubin	Sulfa level	Culture
J. F.	4 mo.	negative	10.6	20,750	43-54-2-0-1	negative	°18 †18	18.7 21.2	– 113	 11.6	 –	 –	 0.15	3.3 7.5 mg.%	negative
D. F.	2 yr.	negative	12.5	8,950	35-62-3	negative	°– † 6	32.2 22.9	– 113	 11.4	 4.19	 1.85	 –	4.8 5.0	negative
S. F.	4 yr.	negative	15.3	9,350	78-22	negative	°17 † 6	14.9 18.7	– 114	 11.0	 4.33	 1.99	 –	5.5 4.5	positive
L. F.	6 yr.	negative	15.3	36,000	88-12	negative	°13 † 7	22.9 22.5	– 106	 11.0	 –	 –	 0.15	3.0 LP 8.1 0 cells Prot 14	positive
D.F.	9 yr.	negative	14.4	11,100	77-21-00-1	negative	°18 †17	22 21.6	– 113	 11.2	 –	 –	 –	5.0 4.8	positive

°Initial studies
†Done about 18 hours after admission

tilled water was started by intravenous infusion. Penicillin and streptomycin were given initially. A telephone call to Colorado four hours later revealed that cultures of the stool from the sibling who had expired had grown out Shigella flexneri, type II. Both the penicillin and streptomycin were discontinued and 0.5 gr. of sulfadiazine per pound was administered subcutaneously every twelve hours. Terramycin was given in a daily dose of 15 mg. per kilogram intravenously. The following day all temperatures were normal. The third day broth and clear liquids were given orally.

J. F., 4 months old; S. F., 4 years old; and D. F., 9 years old, were discharged on the tenth day, two negative cultures having been obtained.

The other children were discharged on the fourteenth day. When oral feedings were resumed, 1 had developed vomiting, and the other child's stool had remained loose.

The laboratory findings in these cases are summarized in table 2. Unfortunately, blood drawn on admission was insufficient to run chlorides. However, several of the children showed aberrations of the blood chemistries. It is strange that the most critically ill patient had the most nearly normal chemistries. Calciums were drawn because of the report that fatal shock in cases of acute shigellosis is accompanied by hypocalcemia. The blood levels for sulfadiazine were all in the same range. A lumbar puncture was performed on L. F. because of the definite though minimal signs of meningism. Although 2 of these children had negative cultures, we must assume that they had the same disease. Rectal mucosa cultures from the father and mother were negative. Cultures of organisms grown were sent to the Minnesota Department of Health. Study of these organisms showed them to be gram-negative, nonmotile bacilli which were morphologically, serologically, and biochemically indistinguishable from Shigella flexneri, type II. All of the blood cultures were negative. Nose and throat cultures revealed no significant pathogens. All chest x-ray films were negative.

SUMMARY

An outbreak of acute shigellosis due to Shigella flexneri, type II is described in 6 siblings, the first of which expired. The successful treatment of the 5 remaining children with sulfadiazne, Terramycin, and parenteral fluids is described.

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Section on PAIN

Use of Levorphan Tartrate for Relief of Postoperative Pain:

Preliminary Report

MARGARET S. EMMONS, M.D., FRED B. GOSLIN, M.D.,
MAX W. SAFLEY, M.D., AND ROBERT T. TIDRICK, M.D.
Iowa City, Iowa

THE PHARMACOLOGIC and analgetic properties of optical isomers of 3-hydroxy-N-methylmorphinan have been studied in animals[1–4] and numerous reports of the clinical effectiveness of the racemate, racemorphan hydrobromide, have been published. Isbell and Fraser[5] were the first to show that in man the addiction liability resides in the levo-optical isomer, levorphan. They also found that doses of 60 to 75 mg. of the dextro-optical isomer, dextrorphan, had no effect on the morphine withdrawal syndrome. Slomka and Gross[6] studied the characteristics of these optical isomers in man and reported that the analgetic properties are confined to the levo isomer. Indeed, evidence pointed to the fact that the dextro isomer interfered with the analgesia produced by levorphan. Since Slomka and Gross employed normal human volunteers and utilized the Hardy-Wolff-Goodell technic, the purpose of this study was to determine the clinical effectiveness of oral and parenteral levorphan tartrate for the relief of postoperative pain.

METHODS

In general, the procedure was much the same as that utilized in an earlier study on racemorphan hydrobromide and morphine conducted in this hospital by Jaggard and associates.[7] Levorphan tartrate was ordered in doses of 1.5 mg. or 3 mg. orally, or 2 mg. subcutaneously, for relief of postoperative pain in general, thoracic, and neurologic surgical patients and administered at the discretion of the nursing staff. The method differed from that of the former study in that no attempt was made to reduce the dosage where indicated. Patients for whom the above doses seemed too large were excluded from the study. The 642 patients who received either morphine or racemorphan hydrobromide in the earlier study served as controls for this investigation.

RESULTS

Table 1 indicates the distribution of patients among the various operative classes in the 2 studies. With the exception of classes 6, 13, and 15, there is less than a 6 per cent difference between the 2 groups. Class 13 constituted 24.8 per cent of the earlier study group, but there were no patients in this class in the present study. However, the analgetic requirements of this class were of a low order (table 4, reference 7). No patients in the previous study were in class 15, whereas 6.4 per cent of those in the present study were in this category. Table 4, reference 7 shows that class 6 has a high analgetic requirement, and, since the per cent of patients in this group exceeds those in the earlier study, we felt that the disparity between groups 13 and 15 was balanced. Accordingly, the 2 studies could be utilized for purposes of comparison.

A total of 416 doses of levorphan tartrate was administered to 110 patients. Of this number,

MARGARET S. EMMONS, *a 1949 graduate of the State University of Iowa College of Medicine, is practicing anesthesiology at Clinton, Iowa.* FRED B. GOSLIN, *a graduate of the State University of Iowa College of Medicine, is a resident in the department of surgery, University Hospitals, Iowa City.* MAX W. SAFLEY, *a 1952 graduate of the State University of Iowa College of Medicine, is in general practice at Forest City, Iowa.* ROBERT T. TIDRICK, *a 1936 graduate of Washington University School of Medicine, St. Louis, is professor and head, department of surgery, University Hospitals, Iowa City.*

371 doses were given for relief of pain. A summary of the analgetic activity of levorphan tartrate as observed in postoperative patients is presented in table 2. The inadequacy of the 1.5 mg. oral dose used initially in the study is indicated by the fact that only 54 per cent of patients obtained relief from pain and 55 per cent of total doses was effective. When the oral dose was increased to 3 mg. in the latter part of the study, 74 per cent of such doses was effective and 64 per cent of patients had relief of pain. The most effective dose and route was 2 mg. of levorphan tartrate given subcutaneously. In this series, 96 per cent of patients experienced analgesia and 96 per cent of total doses was effective.

Untoward effects were observed as indicated in table 3. The proportion of such reactions was greater in those patients who received the drug subcutaneously and who experienced the greatest degree of analgesia.

DISCUSSION

Results from the parenteral administration of 2 mg. of levorphan tartrate are comparable to those obtained in the earlier study conducted in this same hospital and in a similar manner. In that study, 90 per cent of 338 postoperative patients obtained adequate pain relief from administration of 10 mg. or 5 mg. of morphine, and 88 per cent of 304 such patients obtained adequate pain relief from administration of 5 mg. or 2.5 mg. of racemorphan hydrobromide. The smaller doses were given to about one-fourth of the total number of patients because of extremes of age.

TABLE 1
DISTRIBUTION AMONG OPERATIVE CLASSES

Class	*Region*	*Per cent of patients* Morphine or racemorphan hydrobromide*	Levorphan tartrate
1	Head and neck	1.9	1.8
2	Upper abdomen	14.5	19.8
3	Lower abdomen	12.4	10.8
4	Abdominal wall	5.9	11.8
5	Thorax, superficial	3.0	5.4
6	Thorax, deep	7.0	21.6
7	Extremities, soft tissue	7.5	5.4
8	Extremities, bone	6.2	1.8
9	Perineal	7.2	2.7
10	Spinal	2.6	6.4
11	Integument	4.0	3.6
12	Abdominoperineal	1.4	1.8
13	Transurethral	24.8	0
14	Renal	1.9	0
15	No surgery	0	6.4

*Calculated from reference 7.

TABLE 2
EFFECTIVENESS OF ANALGESIA PRODUCED BY LEVORPHAN TARTRATE IN POSTOPERATIVE PATIENTS

Route of administration	*Oral*	*Oral*	*Subcutaneous*
Dose	1.5 mg.	3 mg.	2 mg.
Number of patients	24	28	53
Number of doses given for pain	77	86	208
Range of number of doses per patient	1–20	1–8	1–16
Average number of doses per patient	3.2	3.1	3.9
Number of patients having adequate pain relief	13(54%)	18(64%)	51(96%)
Number of effective doses	42(55%)	64(74%)	200(96%)

The theoretic analgetic equivalent of 5 mg. of racemorphan hydrobromide is 3.2 mg. levorphan tartrate. The subcutaneous administration of 2 mg. doses of the latter provided analgesia in 96 per cent of cases reported in this study. This is a higher degree of effectiveness than would be expected on the basis of previous reports on racemorphan hydrobromide. The enhanced analgetic effect of the levo isomer is explained in the observations of Slomka and Gross[6] who found that the dextro isomer inhibits levorphan and morphine analgesia.

It is quite apparent that the subcutaneous route of administration is more efficient than the oral route, since oral doses of 1.5 mg. provided relief from pain in little more than half the patients, and when the oral dose was increased to 3 mg., 74 per cent of such doses gave adequate analgesia. This was far below the 96 per cent effectiveness obtained from the subcutaneous administration of 2 mg. Perhaps, if we had been less cautious and used a slightly larger dose, the oral preparation would have proved more effective. The average number of 2 mg. subcutaneous doses of levorphan tartrate was 3.9, which is comparable to the average of 3.4 obtained with

TABLE 3
NUMBER OF UNTOWARD REACTIONS TO LEVORPHAN TARTRATE FROM 416 DOSES ADMINISTERED

Reaction	*Number*
Nausea and emesis	8
Drowsiness, excessive	15
Hypotension	4
Pruritus	1
Vertigo	2
Headache	2
Skin reactions	1
Total	33

racemorphan hydrobromide and morphine.[7]

Untoward effects were observed after 7.9 per cent of all doses. This compares favorably with the incidence of 23.7 per cent reported by Keutmann and Foldes[8] after administration of 5 mg. of racemorphan hydrobromide. In the previous study in this hospital, 24.3 per cent of patients receiving racemorphan hydrobromide and 17.1 per cent of those given morphine experienced reactions. Hunt and Foldes[9] reported an incidence of 22.5 per cent after the subcutaneous administration of 3 mg. levorphan tartrate. Glazebrook[10] found that 21.6 per cent of patients receiving 2.6 mg. or less of levorphan tartrate orally experienced untoward effects. On theoretic considerations, the use of a "pure" agent such as levorphan tartrate is to be preferred over the racemate which contains the analgesia-inhibiting dextro isomer. This preliminary report indicates that levorphan tartrate apparently can be used safely and effectively for the relief of postoperative pain.

SUMMARY

1. A total of 416 doses of levorphan tartrate was administered to 110 patients; 371 of these doses were for pain.

2. Doses of 2 mg. levorphan tartrate administered subcutaneously provided satisfactory postoperative analgesia for 96 per cent of patients.

3. When given orally, doses of 1.5 mg. provided adequate pain relief for 55 per cent of patients, and 3 mg. for 7.4 per cent.

4. Levorphan tartrate compares very favorably in terms of safety and effectiveness with pharmacologically equivalent doses of racemorphan hydrobromide.

Levorphan tartrate and racemorphan hydrobromide are generic names of Levo-Dromoran Tartrate and racemic Dromoran Hydrobromide, respectively, and were made available by Dr. M. J. Schiffrin, Hoffmann-La Roche, Inc.

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Management of Headache

Vascular or tension headache, caused by distention of intracranial blood vessels, is the type of headache seen most frequently in the practitioner's office. The ultimate cause of these headaches is unknown, but emotional pressure, fatigue, and anxiety are known to predispose to the syndrome.

Migraine, the most severe vascular type of headache, is pain in one side of the head that shifts to the entire head. In later attacks pain may affect either side of the head. After the initial onset, the pain characteristically builds up to nausea, vomiting, pounding, and pain in the affected eye. Scotoma and paresthesia sometimes appear during the height of the pain. If taken early, oral Cafergot may abort the pain. After pain becomes severe, a strong sedative or even codeine may be necessary. Attention to the patient's emotional problems by a sympathetic physician may help to alleviate some of the underlying predisposing emotional factors.

Because headaches may also be the first sign of organic disease, each patient with headache should be approached as follows: (1) thorough history, (2) neurological examination, (3) skull, sinus, and cervical spine roentgenograms, (4) lumbar puncture, if expert opinion fails to find contraindications, (5) angiography or pneumoencephalography if indicated, and (6) psychiatric help if usual supportive measures fail.

David J. LaFia, M.D.: The Practical Management of Headache and Other Head Pains. Rhode Island M. J. 37:147-150, 1954.

Procaine Injections for Painful Musculoskeletal Conditions:

A Fifteen-Year Follow-up*

RALPH L. GORRELL, M.D.

Clarion, Iowa

More than 900 patients with painful muscular and skeletal conditions have been injected with procaine solution. This paper is a fifteen-year summary of this clinical experiment, the types of patients injected, and the results obtained.

PERSONAL INTRODUCTION TO PROCAINE INJECTIONS

Appropriately enough, I was the first patient. In 1936, I strained my low back. When the pain did not respond to limited activities or simple therapy, I began the round of orthopedic consultations. An internationally known orthopedic surgeon advised fusion of my lumbar spine, in spite of the fact that I had always participated in sports and had not suffered from back symptoms previously.

A medical consultant in the same clinic, who had carried on clinical research in arthritis for many years, advised against fusion and suggested deep massage to fibrositic nodules followed by infrared therapy. This was my first introduction to the fact that pain means different things to different specialists.

The massage and infrared gave good temporary relief but the pain recurred. At this time I read Leriche's book on treatment of pain[1] and Thomas Lewis article[2] on the origin of pain. The points of pronounced tenderness in my back were injected with 1 per cent procaine solution. The back pain was relieved at once and has never been as severe since. I still have fibrositis which has required 2 other injections of procaine in the intervening eighteen years, but I have participated in tennis, golf, swimming, and active medical practice without disability. None of my patients who have had low-back fusions or protruded intervertebral disks removed returned to full activity thereafter.

I am happy that a portion of my tibia was not transplanted into my lumbar spine and that my back is flexible and free from scars, which can themselves cause pain. Possibly occasional pain is the price we pay for flexibility. Is the price too high?

I have gone into a little detail about my own case, primarily because it is a summary of what happens to many patients who experience pain.

SERIES OF PATIENTS

These patients were seen in the course of general practice and represent unselected individuals who sought pain relief. Toward the end of the series, several were directed to our office for injection therapy, so that the totals are more than would be expected in the more routine general practice.

For each patient treated by injection, there were two or three who were treated by other methods, including:

1. Ethyl chloride spray applied locally.
2. Support—(a) adhesive tape, stiff or elastic, (b) plaster casts, and (c) permanent wearing of support (rarely).
3. Heat—(a) diathermy, (b) infrared, and (c) counterirritants.
4. Vasodilatation—(a) systemic injections of nicotinic acid or tetraethylammonium (Etamon), or Priscoline, (b) heat to extremity above lesion, and (c) contrast baths; paraffin applications.
5. Rest, exercises, or both.
6. Analgesics including salicylates, Butazolidin.
7. Cervical traction for neck and shoulder pain.

RALPH L. GORRELL, *a 1933 graduate of Stritch School of Medicine of Loyola University, Chicago, is in medical practice at Clarion, Iowa.*

*Presented to the Latin-American Congress of Physical Medicine, at Medellin, Colombia, February 17, 1954.

TABLE 1
TOTAL PATIENTS TREATED WITH PROCAINE INJECTIONS

Men	561
Women	372
Total	933

8. Removal of cause where possible.
9. ACTH or cortisone (rarely).
10. Rarely, vitamin B_{12}, bacterial vaccines, bee venom.

Controls. The groups of patients who were treated with and without injections give somewhat of a control, but it is difficult to establish exact control. An old man with osteoarthritis, fibrositis, and poor posture cannot be compared to a young man in good health, yet both may have sciatica. A nervous member of a highly nervous race cannot be compared with the stolid and phlegmatic individual, even though both have subdeltoid bursitis.

The same patient, in succeeding years, may suffer from several pain syndromes and receive injection therapy. In this case, he is his own control.

Statistics. Attached tables indicate the total number of patients, their ages, sex, location of pain, cause of pain, number and type of injections, results of injection, and recurrences.

The tendency is to think of men having far more injuries and painful skeletal conditions than women. In this series, 561 men and 372 women were treated with procaine injections (table 1).

Almost one-half of all patients were grouped between the ages of 30 and 60 (table 2). The younger patients suffered primarily from trauma and the middle-aged from degenerative processes. Even in the teens, however, fibrositis is not uncommon, and osteoarthritis may be far advanced in the 40's.

TABLE 2
AGE OF PATIENTS RECEIVING PROCAINE INJECTIONS

Age groups	*Number of patients in each age group*
1 to 10	1
10 to 20	47
20 to 30	104
30 to 40	135
40 to 50	185
50 to 60	155
60 to 70	110
70 to 80	37
80 to 91	6

Location refers to the area in which the patient felt pain, not necessarily the location of the trigger point (table 3). Of these patients, one-third were suffering from back pain. Many had run the gamut of conservative and surgical therapy.

The underlying causes of pain (table 4) are listed rather carefully and any organic diagnosis has been substantiated by operation, biopsy, postmortem, appropriate laboratory procedure, or consultation. The great majority of these patients have an inherent cause of pain, that is, fibrositis and osteoarthritis. Table 5 lists the numbers and type of injections.

TABLE 3
LOCATION OF PAIN

Back	288
Coccyx, sacrum	8
Head, face	30
Chest	98
Shoulder	105
Arm	7
Elbow	16
Hand	15
Thumb, fingers	5
Neck	72
Abdomen	33
Inguinal	3
Hip	24
Leg	59
Sciatica	58
Knee	64
Foot, toe	23
Scar, surgical	16

The results obtained are listed in various classifications: 655 patients were relieved of the pain completely, 169 experienced incomplete relief, and 54 obtained no benefit or the pain was temporarily increased (table 6).

These results were obtained without any other therapy preceding the injection. As a rule, no barbiturates were given. No patient was told that the injection would cure him. The dramatic effect of the injection may have had some psychologic effect. Psychiatrists might believe that the discomfort of the injection would appeal to some minds.

On this point, I can do no better than quote my favorite author, "One should not inject any patient who gives a history of a nervous breakdown, who complains of symptoms from head to toes, who is receiving compensation and enjoying it, who cannot accurately localize the pain, who does not honestly want relief of pain because it would mean that he must again as-

sume household duties or daily work, who gives the clinical impression of having a psychopathic personality or of being constitutionally inferior. . . . If the patient is looking for sympathy from friends and family, for a vacation, for an excuse to avoid the distasteful, i. e., coitus, for continuance or increase of pension or compensation, he should not be injected. Such patients do not genuinely wish relief and will not admit it, if obtained. They will, rather, seize upon the injection as another cause of pain." [3]

The preceding failures are due to the patient. Failures due to the physician include: (1) trigger point not found, (2) if found, not completely infiltrated and not injected deeply enough, (3) a minor trigger point not found after major point blocked, (4) injection of area of referred pain which gives relief only for a limited time, (5) incomplete diagnostic effort did not reveal other diseases or the causative condition itself, (6) failure to follow the patient and to reinject, if necessary, (7) failure to explain to the patient the occasional sharp, temporary exacerbation which may occur in three to twelve hours and to give an analgesic in readiness for this event, (8) failure to obtain full information. For example, a man of 44 had a protruded intervertebral disk removed at a university hospital, and later in our office was given several sympathetic blocks for persistent pain. Not until we searched for a cause did we learn that he had been a patient in a psychiatric hospital between surgical and injection therapies.

TABLE 4
CAUSES OF PAIN

Trauma, direct	100
Trauma, direct, old	20
Trauma, indirect (twisting, jerking)	145
Sprains of joints	40
Strain (only)	16
Infections, acute 6, chronic 8 (residual points)	14
Fibrositis (rheumatism)	394
Osteoarthritis (physical and x-ray demonstration)	102
Bone lesions, osteoporosis 8, spondylolisthesis 1, gout 6, fracture of spine 5, rheumatoid arthritis 6	26
Intervertebral disk, proved	21
Neoplasm, metastatic	10
Peripheral vascular disease	8
Frostbite 2, thrombophlebitis 7, Raynaud's disease 2	11
Psychogenic (emotional basis)	25
Neck, stiff	13
Unknown	39
Scar, surgical incision (abdomen, chest, extremities)	22
Cervicitis	12
Brain, thrombosis	8
Miscellaneous: lipoma back excised 3, trigeminal neuralgia 4, peptic ulcer 4, true bursitis 9, gallstones 2, tenosynovitis 3, migraine 3, cervical polyp 2, herpes zoster and other rare causes 25	55
Total causes (more than one in several patients)	1,081

TABLE 5
NUMBER AND TYPE OF PROCAINE INJECTIONS

Local injection of trigger points	
Patients receiving 1 injection only	648
Patients receiving 2 injections	170
Patients receiving 3 injections	53
Patients receiving 4 injections	24
Patients receiving 5 injections	9
Patients receiving 6 injections	6
Patients receiving 7 injections	4
Patients receiving 8 injections	2
Patients receiving 9 injections	1
Patients receiving 10 injections	1
Patients receiving 13 injections	1
Total number of local injections	1,400
Block procedures	
Stellate block	33
Brachial plexus block	7
Lumbar sympathetic block	15
Caudal block (early part of study)	6
Sciatic block	14
Femoral block	2
Intercostal block	15
Total number of blocks	92

FOLLOW-UP OF PATIENTS

Long-term follow-up on injected patients indicates that some "cures" did not persist for more than a few days. Contrarily, some patients, not thought to have benefited much at the time, reported months or years later that relief had been prolonged. Underlying disease appears, such as multiple myeloma, metastatic neoplasm, or multiple diseases are eventually recognized.

Frequently a patient remarks that 1 injection, given years ago, entirely relieved the pain and that he had experienced no recurrence. Sprains which were well injected did not result in weak or painful joints.

Curative procaine injections need not be re-

TABLE 6
EFFECT OF PROCAINE INJECTIONS

Dramatic pain relief	69
Good pain relief	586
Fair pain relief	169
Poor or no relief	54
Good but transient relief	29

Dramatic pain relief: immediate, complete relief of pain after failure of previous therapies for days, weeks, or months. Good pain relief: complete or practically complete pain relief which persisted. Fair pain relief: pain decreased but not completely, or completely but recurred in a few days or weeks. Poor or no relief: little or no effect, usually due to wrong injection or wrong patient. Good but transient relief: These would be listed under good pain relief, except that follow-up showed pain relief lasted only a few hours or a day.

peated more than twice. The pain relief must last at least four to six hours after the first injection and a longer period after the second injection, if the trigger point has been well injected.

If 2 or 3 injections do not provide pronounced relief, the injections should be stopped and the entire problem studied again. This is a good idea for any patient management, of course. Multiple diagnoses become apparent, as the patient is found to have combinations of osteoarthritis, fibrositis, osteoporosis, cervicitis, prostatitis, occupational overstrain, or poisoning.

Looking back over the records, I am well satisfied with the results of procaine injections given when patients need such injections.

TECHNIC

The technics of sympathetic blocks of the stellate ganglion and lumbar sympathetic chain are standardized and described in all textbooks. Moore's[4] straightforward text on "Regional Block" provides a very clear description of every standard nerve block. "The Management of Pain" by Bonica[5] is a storehouse of information on the treatment of painful conditions by all technics. Both books describe sciatic, femoral, and brachial blocks.

Trigger point. The above specialized procedures are needed only occasionally. All that is needed for treatment of trigger points is sufficient knowledge of anatomy to avoid penetrating the few danger points in the body. In most regions of the body, a thin — gauge 21 to 23 — sterile, flexible needle can be introduced without risk. A blood vessel can be punctured without harm if procaine solution is not injected. If the solution is injected as the needle is slowly moved forward, the vessel is usually pushed out of the way. Care must be taken, however, not to puncture a lung and possible pneumothorax.

Pain originates from a trigger point. The trigger point is a small area of irritation located in connective tissue[6] from which pain travels outward. The pain usually does not follow anatomic nerve distributions.

Cause of the trigger point. Direct trauma such as a blow; indirect trauma, such as sprain, strain, or twist; fibrositis or muscular rheumatism; osteoarthritis; acute or chronic infections including upper respiratory infections; or underlying organic disease may set up trigger points. In the latter instances, the diagnosis and treatment is that of the primary disease. Procaine injections may be used palliatively during the disease, or afterward, to remove the residual trigger points.

What it is. The trigger point has not been exactly duplicated in clinical experiments. Kellgren[7] has injected hypertonic saline solution into the muscles and fascia of volunteers and has thus demonstrated that certain pain patterns regularly follow. Histologic study cannot be performed because the trigger area cannot be excised. The clinical explanation is that a small area may become a miniature sending station for pain, if anatomically or physiologically altered.

The point may be in the skin, but usually such points are areas of referred pain. It may be located just subcutaneously or 4 in. (10.16 cm.) deep in muscle. It is usually small. It may be found in apparently normal tissue or in a nodule of fibrositic tissue. In this series, long-term follow-ups of patients who have had fibrositic nodules removed from the low back show that the pain has always returned if the underlying cause was not removed.

Why do procaine injections help? Why does the local injection of a short-acting drug stop a process which may have gone on for weeks or months? Leriche[1] suggested that all pain is due to vasospasm. According to Travell,[8] any type of injection or even needling modifies the trigger point. The literature records the injection of iodized oil (Lipiodol), morphine solution, isotonic sodium chloride solution, bee venom, cortisone, and many other chemicals with apparent pain relief. Ethyl chloride sprayed over the skin covering the trigger point gives pronounced relief in acute stiff neck and sprains.

Finding the trigger point. The patient who has suffered from a direct blow is quickly relieved if the site of injury is infiltrated or the most tender point within that area.

The sprains, strains, and tears of ligaments and muscles produce trigger points proximal to the injury. If injected at once, the swelling of the sprained joint does not appear.

Fibrositis, periarthritis, rheumatism, osteoarthritis, and other less definite conditions usually cause pain in the back, gluteal areas, neck, or shoulder. Pain in the abdomen may radiate out from a trigger point in the back muscles. Abdominal injections are usually not given until all abdominal disease has been ruled out, trigger points have not been found in the paraspinal muscles, and a sedative used for neurogenic or "spastic" colon.

Trigger points are to be found in the lower back muscles (erector spinae, multifidus) and ligaments, gluteus muscles, strap muscles of the

neck below the occiput, and in the deltoid, supraspinatus, or trapezius. Travell[8] has sketched the trigger points for various pain locations. The patient must wince when the trigger point is palpated. Identification is more assured if the patient states that such palpation causes the pain to recur. Infiltration of a true trigger point relieves pain completely.

The more numerous and tender the areas that are found, the less likely it is that they are true trigger points. If no trigger point can be located, the painful area should be sprayed with ethyl chloride solution 10 to 15 times, very gently with a light spray, avoiding freezing. If complete relief is obtained, no further therapy is required. Pain is usually somewhat relieved and motion increased, so that true trigger points can be more readily found.

Why treat the trigger point? If untreated, the trigger point may gradually lose its sensitivity and may remain indefinitely a constant source of irritation and pain or may cause increasing pain. The patients say that they "have to be careful of that back" ever since the injury or lumbago. They claim the sprained ankle is weaker than formerly and sprains again more readily. The shoulder hurts on less provocation. These sequelae are unknown to the first physician who treated the patient with conventional heat, support, and analgesics.

In suitable cases the trigger point should be relieved by injection because in no other way can a pathologic process be reversed so quickly, so completely, and so permanently. This statement, often ridiculed by orthopedists, has been proved by this long-term follow-up.

Results of injection. The injection or infiltration of a true trigger point results in immediate pain relief and resumption of full activity. The patient can move and assume positions that were impossible or painful before the injection, thus furnishing objective evidence. This relief occurs even when patients are not told to expect it. Patients who were given injections during the diagnostic procedures had just as high a percentage of cures. This helps to rule out placebo effect.

The patient should be warned to expect a sharp recurrence of the pain in two to eight hours after injection, and should be given several analgesic capsules to take, if needed. Such an exacerbation occurs in 40 per cent of patients. Reinjection is done if permanent relief is not obtained.

Technic. Instead of raising a bleb or wheal in the skin, after the manner of the anesthetists, Travell[9] suggested that a quick puncture through the skin is less painful. The needle should be slowly pushed through the insensitive fat until a little resistance is furnished by fascia. Injection is begun slowly before the patient complains of pain, and several cc. of solution are infiltrated. Then deep tenderness is elicited by pressing firmly around the needle. If hard pressure does not cause pain, the trigger point has been injected and the needle is quickly withdrawn. If deeper tenderness is elicited by pressure, the needle is slowly introduced until tenderness again appears and infiltration is again begun. The process is repeated until all tenderness is gone or bone is reached in extremities or back. In this manner, the patient feels only one jab with the needle.

A weak solution of procaine is used, usually ½ of 1 per cent. Epinephrine (Adrenalin) is not used as a patient in pain is made more susceptible by this drug, and all patients dislike the tachycardia. In a few cases, long-acting local analgesics were used without materially affecting the results.

Complications. True procaine sensitivity is so rare that it can be disregarded. Inadvertent procaine injection into a vein makes the patient dizzy and syncopic if he is sitting up. This can be prevented by giving a barbiturate one-half hour before the injection or corrected by giving a barbiturate intravenously or intramuscularly. Parenthetically, the vogue of using procaine intravenously is declining since the studies of Beecher[10] have shown that the analgesia obtained by intravenous procaine is no better than that obtained by giving pentobarbital sodium and "was achieved at the cost of tremendous side-action liability, mainly unpleasant . . . extreme anxiety and apprehension, dyspnea, tachycardia to 150 a minute, the disorientation and the violent vomiting." It is effective in some cases of generalized itching.

Psychic complications appear in susceptible patients if they are allowed to witness the preparation of the injection tray or introduction of the needle. The patient should be lying down on a table. The physician interposes his body between the patient's eyes and the area to be blocked, or turns the patient's head or body away.

After the patient is positioned, the trigger point is palpated again and marked with a skin marking pencil to avoid the complication of having the point move while changing position.

A number of authors not mentioned in this article have investigated procaine injections.[11–14]

CONCLUSIONS

A fifteen-year survey indicates that procaine injections may cure muscle-fascia pain due to local or systemic causes. Such cures are often dramatic and usually permanent unless the cause is still operative and to be obtained in no other way. Careful study of the patient should precede such injections. Complications are very rare and mild. Several hundred more injections have been given since January 1, 1954. This increases totals but does not change conclusions.

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Editorial

All inquiries and manuscripts for the Section on Pain should be sent to Dr. John S. Lundy, 102 Second Avenue S.W., Rochester, Minnesota, or to the Editorial Department, The Journal-Lancet, *84 South Tenth Street, Minneapolis 3, Minnesota.*

BOLD WAR AGAINST PAIN

A very encouraging trend in the investigation of drugs is the preparation and use of special agents for the relief of pain, as will be seen in the paper, "Use of Levorphan Tartrate for Relief of Postoperative Pain: Preliminary Report," by Emmons and associates. Clinicians themselves will benefit from a ready knowledge of the advantages of one form of a drug over another. Some of the most interesting of recent studies being made indicate that trials are under way to combine two drugs, such as Nisentil, with Nalline, in the hope that Nalline will neutralize the respiratory depressant effect of Nisentil without interfering with the ability of Nisentil to relieve pain. Similar efforts are being made with other drugs.

In the current article on levorphan tartrate, the difference in the addictive properties of the levorotatory product as opposed to the dextrorotatory product is shown. This is of real interest. It is with satisfaction that in the Section on Pain we include the paper referred to above, as well as a paper in which attention is called to clinical evaluation of a procedure which has been talked about much, but which seldom has been presented from the standpoint of a long-time follow-up. These matters are of much practical value.

John S. Lundy, M.D.

Book Reviews on Pain

NERVE BLOCKS: A MANUAL OF REGIONAL ANESTHESIA FOR PRACTITIONERS OF MEDICINE, by John Adriani, M.D., director, department of anesthesiology, Charity Hospital of Louisiana; professor of surgery, Tulane University of Louisiana, School of Medicine; associate clinical professor of surgery, Louisiana State University School of Medicine, New Orleans, Louisiana, 1954. Springfield, Illinois: Charles C Thomas. 265 pages. Price $6.50.

In the preface the author has indicated the purpose of his book as follows: "This manual has been prepared for those who are beginners in the study of regional anesthesia. It is also designed for those whose chief interest is not regional anesthesia but who are called upon to perform an occasional block. The manual is by no means comprehensive or complete. Only the most important and commonly used blocks are described. Its outline form is designed for those who desire at a moment's notice the substance of a given topic together with all pertinent details concerning hazards, precautions and causes of failure. Obviously those who wish to master the subject of regional anesthesia and become experts must pursue their studies further in the anatomy laboratory on cadavers, manikins and on prepared dissected specimens, or in more detailed textbooks on the subject."

This book is especially appropriate for those persons who wish to use regional local anesthesia and who are particularly concerned with diagnostic and therapeutic blocks. The book is well written, well illustrated and adequately indexed. It is easily read and has a distinct advantage in the condensation of the remarks made concerning a given block, that is, what the block is used for, how it is done, what agents are used and the dose, quantity, and concentration of the solution. This book appropriately emphasizes a most practical approach to the problem of diagnostic and therapeutic blocks.

John S. Lundy, M.D.

(Continued on page 38)

BOOK REVIEWS ON PAIN
(Continued from page 37)

INHALATION THERAPY AND RESUSCITATION, by Meyer Saklad, M.D., director, department of anesthesiology, Rhode Island Hospital, Providence, Rhode Island, 1953. Springfield, Illinois: Charles C Thomas. 343 pages, 130 illustrations. Price $7.50.

This book and the place it fills constitute a demonstration of how important it is that someone, with the capacity and experience requisite to the assignment, devote enough time and effort to cover the subjects of inhalation therapy and resuscitation. It is only in this way that such a subject can be presented adequately.

The need for such a text should be apparent at once. First of all, if the student is to acquire an adequate understanding of the subject, his first demand is a text that will present it to him clearly and extensively. Second, if he is to be faced with examinations given by various specialty boards, as he probably will be, the members thereof are certain to ply him with questions about respiratory physiology and the application of his knowledge in that field to clinical practice.

This book is a very valuable contribution because it fulfills a need that previously had not been satisfied. It may be studied with profit by both physicians and those associated with them who are concerned with problems involving the physiology of respiration.

The paper used is excellent. The printing is good. The book has an excellent bibiliography of 402 references and is adequately indexed.

John S. Lundy, M.D.

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THE PAINFUL PHANTOM: PSYCHOLOGY, PHYSIOLOGY AND TREATMENT, by Lawrence C. Kolb, M.D., section of psychiatry, Mayo Clinic, Rochester, Minnesota, 1954. Springfield, Illinois: Charles C Thomas. 50 pages. Price $1.50.

This very useful dissertation on the painful phantom — psychology, physiology, and treatment — is highly desirable reading. An excellent list of references is given, and the presentation of case reports emphasizes the points that the author wishes to make. For those who are interested in the problem of pain, this discussion will be thoroughly enjoyed.

John S. Lundy, M.D.

Current Literature on Pain

PAIN CAUSED BY POTASSIUM INTOXICATION IN A PATIENT WITH KIMMELSTIEL-WILSON SYNDROME. William E. S. James, M.D., Paul E. Wisenbaugh, M.D., and Norman P. Shumway, M.D., J.A.M.A. 153:545-546, 1953.

A case is reported of an unusual type of pain associated with potassium intoxication in a patient with Kimmelstiel-Wilson syndrome.

Upon admission to the hospital, the patient, a diabetic with renal disease had, with the exception of hypertension, all the symptoms characteristic of this nephrotic syndrome: oliguria, azotemia, edema, and hypoproteinemia. Severe aches and cramping pains in the legs, which spread to the rest of the body, were accompanied by extreme weakness and abnormal electrocardiographic changes.

Substitution of regular insulin for protamine zinc insulin and glucose administration decreased the serum potassium level and relieved the pain. The use of fluids rich in potassium, such as orange juice and broth, should be avoided in the treatment of insulin reactions since hyperkalemia may occur.

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WINTER ACHES AND PAINS. K. M. Robertson, M.D. Practitioner 171:613-618, 1953.

Pain associated with coronary disease, peripheral vascular disease, headaches, arthritis, fibrositis, neuralgia, respiratory infections, paraesophageal hernia, duodenal ulcer, urinary bladder neck obstruction, and various sorts of trauma are accentuated or may begin during the winter months.

Cold, physical activity, emotional stress, and heavy meals are well-known factors which may initiate anginal pain. Unusual manifestations of angina, such as retrosternal discomfort, pain in the back or arms, pain in the throat and lower jaw should not be overlooked or serious complications may result. Anticoagulants for the treatment of cardiac infarction and acute coronary insufficiency have proved to be of value. Nitroglycerin remains the most useful drug in the symptomatic control of angina, though good results have been obtained with Pentaerythritol Tetranitrate.

Complications of peripheral vascular disease, such as intermittent claudication, trophic complications, chilblains, erythrocyanosis, and Raynaud's syndrome, are adversely affected by cold and damp weather. Sympathectomy is widely used for Raynaud's syndrome and peripheral vascular insufficiency. Tolazoline has proved effective for chilblains, while erythrocyanosis often responds to weight reduction and use of nicotinic acid and thyroid extract.

The hypertensive individual may have more headaches during the winter, although other factors, perhaps psychogenic, surely play a contributing role. Cold may be a trigger mechanism which determines the pain of trigeminal neuralgia.

Degenerative arthritis, benign fibrositis, malignant osteitis secondary to prostatic or bronchial carcinoma, and Paget's disease may present symptoms similar to one another and become increasingly severe during winter months. Since obesity aggravates these conditions, the patient must be particularly vigilant over his intake during cold weather as there is a tendency to gain weight at this time. Soft-tissue pains, often accentuated by cold, respond well to rest, physiotherapy, analgesic injections, and use of salicylates. Myxedema, a common cause of rheumatic symptoms, often appears for the first time in

winter as a result of reduced thyroid activity. Many patients require an increased dose of thyroid extract in December.

The lightening pains of tabes, the postherpetic syndrome, and the nerve root irritation syndrome all become more severe during the cold months. The patient afflicted with these disorders may prevent recurrences by dressing as warmly as possible.

Tracheitis can easily be mistaken for angina, since discomfort due to this condition is increased by walking in the cold. Care in taking the history and judicious use of electrocardiography should help to avoid such a mistake. All forms of pleurisy tend to increase in cold weather. Early tuberculous pleurisy, the pleurisy overlying a pneumonic, atelectatic or malignant segment of lung may easily be diagnosed as less serious conditions. Chest films should be taken of most patients with pleuritic aches and pains.

Few pains are confined exclusively to the winter months and in most cases are simply accentuated by the cold weather. Pain of visceral origin seems less influenced by the season than pain of skeletal and vascular origin.

Diagnostic oversights can be avoided only by constant vigilance on the part of the physician and an awareness of the fact that errors are more easily made in winter when pain becomes a particularly prominent symptom.

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RELIEF OF POSTOPERATIVE PAIN. Harrell C. Dodson, Jr., M.D., and Howard A. Bennett, M.D. Am. Surgeon 20:405-409, 1954.

In a study to determine the requirements for postoperative drugs, only 55 per cent of 335 patients recovering from major surgery needed a pharmacologically active drug to alleviate pain if placebos were used.

If injection of placebos proved ineffective after ten to fifteen minutes, an analgesic agent, usually meperidine, was then given. The total dosage of meperidine, or its equivalent, given during the first seven postoperative days was considered the required quantity of analgesics.

Less than one-half of the 55 per cent of patients who required drugs needed more than 100 mg., and only 6 per cent of the entire group of patients required more than 300 mg. of drugs. Placebos were completely effective in 15 per cent of the 335 patients and 30 per cent required neither placebos nor analgesics for pain relief.

Abdominal and thoracic surgical procedures required more drugs than did other major surgery. Of the 194 patients undergoing abdominal or thoracic operations, only 32 per cent did not need analgesics, while 9 per cent required more than 300 mg. of the drug. In contrast, of the 141 patients undergoing other major procedures, including thyroidectomy, radical mastectomy, and amputations, 62 per cent did not require drugs and only 1.4 per cent received more than 300 mg.

In a group of patients who had abdominal or thoracic surgery prior to the placebo study program, 95 per cent required analgesics.

The quality of the nursing staff is a most important factor in allaying postoperative pain without narcotics, emphasizing the psychosomatic aspect of this period.

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NISENTIL IN OBSTETRICS, by Perry O. Powell, Jr., M.D., and John E. Savage, M.D. Obst. & Gynec. 2:658-660, 1953.

Excellent results have been obtained in obstetrics with subcutaneous or intravenous injections of Nisentil. The drug causes the patient to become drowsy, anxiety-free, and cooperative. The effect lasts one and one-half to two and one-half hours and produces negligible amnesia unless used with scopolamine. Patients experience euphoria but have no pupillary effect or respiratory depression. Analgesia is rapid and fetal depression seldom occurs.

Of 125 obstetric patients, 106 who received subcutaneous injections of Nisentil in 60-mg. doses or more reacted in 5 to 15 minutes. Intravenous doses of 30 to 60 mg. given to 19 patients were particularly effective for the multipara because analgesia was obtained in about two minutes. A single injection sufficed for 85, while 40 required repeated doses up to 240 mg.

Scopolamine was administered with Nisentil in doses of 0.32 to 0.6 mg. intravenously or subcutaneously. Saddle block anesthesia was usually employed for delivery.

Of the total number of patients, 101 obtained full analgesia; 19 showed moderate results; and 5 patients experienced no relief. The average length of labor among the 90 multiparae was six hours and twelve minutes; for the 35 primigravidae, ten hours and six minutes.

Among 126 babies delivered, 12 were mildly depressed and required mild physical stimulation; 7 were blue, requiring ten to thirty minutes in the Bloxsom airlock; and 2 were anoxic, severely cyanotic and limp, but recovered after thirty to sixty minutes in the airlock. None of the 19 mothers given intravenous injections had depressed babies.

Side effects which occurred in a few patients included dry throat, disorientation, excessive perspiration, and hypertension.

The Billroth I Gastric Resection, by Horace G. Moore, Jr., and Henry N. Harkins, 1954. Boston: Little, Brown & Co. $7.50.

As may be inferred from the title, this book is written primarily to advocate the Billroth I gastric resection over the alternative method, the Billroth II operation. The authors describe their technic, with acknowledgments to various surgeons for certain aspects of this method, and maintain that the Billroth I anastomosis is almost always feasible for either ulcer or carcinoma regardless of the extent of resection. For the Billroth II anastomosis, these authors claim better physiologic function with less tendency to postoperative anemia and hypoglycemic syndromes. Much evidence is produced to show better mixing of food, slower gastric emptying, and decreased fecal fat and nitrogen after the Billroth I gastric resection. The authors state that in their conscientiously compiled statistics the incidence of the dumping syndrome is almost equal in the two types of gastric resection, although probably the general impression among the majority of surgeons is that dumping occurs less in the Billroth I cases.

The book contains much general information on gastric physiology, preoperative and postoperative care, indications for surgery, and other matters which should be of value to the surgeon interested in subtotal gastric resection of any type. Considerable support is drawn from current and recent literature throughout the book.

Arthur W. Ide, Jr., M.D.

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The Praictical Management of Diabetes, by Edward Tolstoi, M.D., 1953. Springfield, Illinois: Charles C Thomas. $3.25.

This well written monograph presents the author's views on the practical management of diabetes. To one who has seen the therapy of diabetes through the cycles of preinsulin days from the starvation diet of Allen to the normal caloric intake allowable with insulin, the contrast in treatment is striking. The treatment of diabetes must always be somewhat of a compromise, and replacement therapy should never be expected to equal the physiologic production of insulin in the normal patient. The therapeutic purist will attempt the impossible in trying to control both hyperglycemia and glycosuria. The pathologist may maintain that any and all treatment falls short of altering appreciably the inexorable vascular and other lesions of the disease. The internist often realistically accepts less than complete laboratory control, and minimal occasional glycosuria is accepted as preferable to complete control of glycosuria with increased tendency to insulin reactions. Many physicians will accept only in part the liberality of the diet suggested in this monograph.

C. A. McKinlay, M.D.

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The Jealous Child, by Edward Podalsky, M.D., 1954. New York City: Philosophical Library, Inc. $3.75.

The foreword and first two chapters of this book cover the mental and physical development of the individual and his adaptation to society as a functional unit. Causes of jealousy are then outlined and enlarged upon from the standpoint of physical, health, racial, social, economic, and family situations. Each chapter is organized to cover first the situation, then how it creates jealousy, and finally various measures are suggested which can be taken to control it.

I feel that the chapters dealing with rheumatic fever, tuberculosis, diabetes, obesity and glandular defects could all have been considered under the one heading of disabling diseases. A rather morbid picture of these diseases is painted which seems to reflect the types which would be seen in a teaching institution. The majority of children with the above mentioned ailments would lead a normal life, and only a select few would be in a situation which would be apt to produce jealousy.

The remaining chapters cover left-handedness, speech defects, deafness, epilepsy, maladjustment, sibling rivalry, twins, unwanted children, divorced parents, adoption, illegitimacy, occupation of parent, minority, only child, and step child. The author handles these situations well and gives a great deal of insight into the problems they produce. All of these situations produce jealousy in some children and the ideas at the end of each chapter on how to prevent or overcome the symptoms are excellent. The last chapter bears the same heading as the title of the book. This closing chapter is a good resumé of the subjects which are discussed throughout the book.

The Jealous Child is not a book for parents or lay people to use as a means of self treatment. It is a guide for those with a background of training who deal with children and parents in the situations discussed. For this group, it would be a worthwhile addition to their library.

Theodore S. Smith, M.D.

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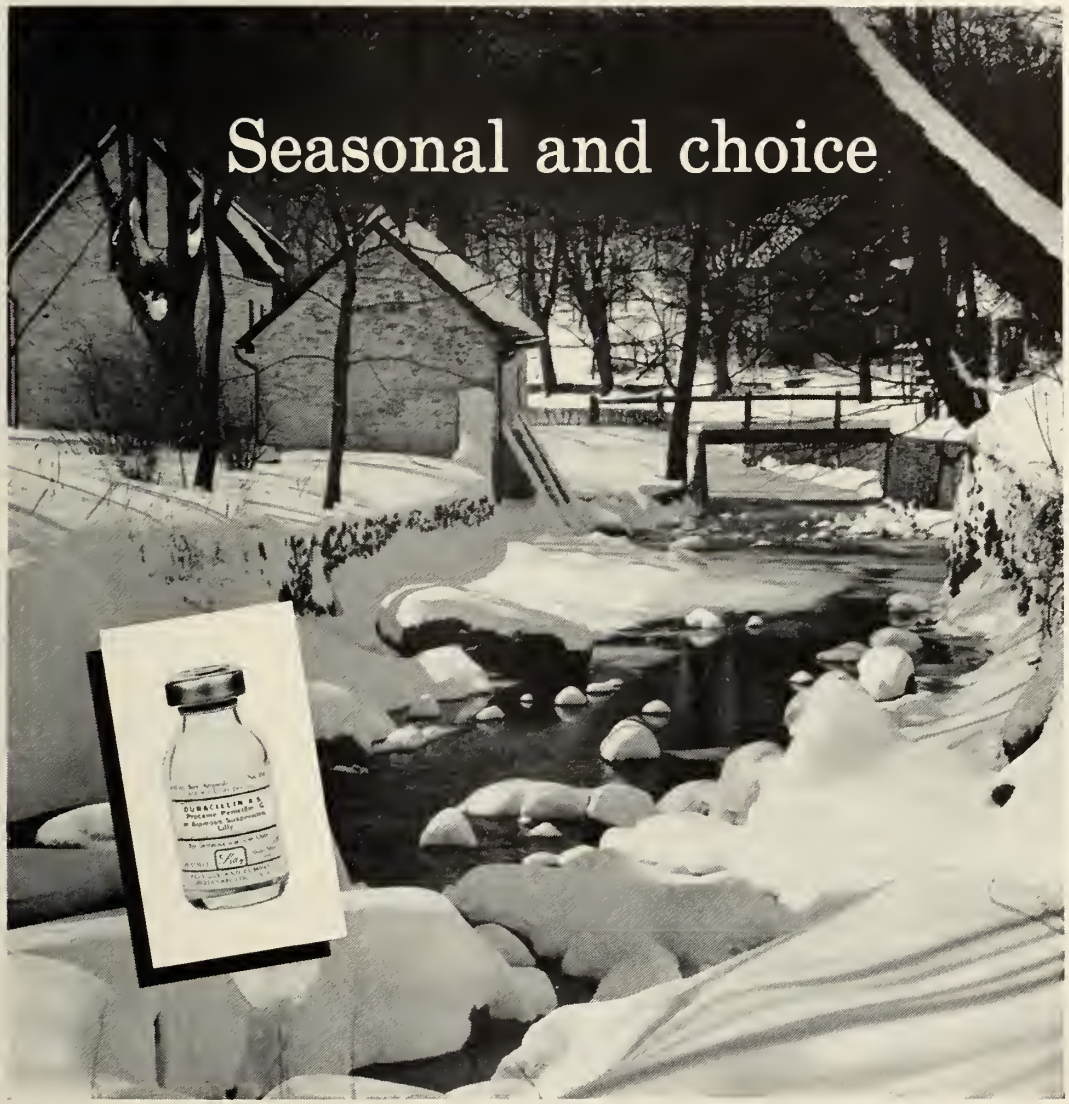
An Atlas of Congenital Anomalies of the Heart and Great Vessels, by Jesse E. Edwards, Thomas J. Day, Robert L. Parker, Howard B. Burchell, Earl H. Wood, and Arthur H. Bulbulian, 1954. Springfield, Illinois: Charles C Thomas, 202 pages, 491 illustrations. $12.50.

This is an admirable book which will be a welcome addition to the libraries of both advanced and beginning students of congenital heart disease.

There are 30 sections in the book, each of which covers 1 anatomic variety of congenital heart disease briefly and systematically. In each section an introductory explanation of the disease is followed by photographic illustrations, usually both of models and the original specimens from which the models were made, and a case history. This is followed by a summary of the clinical features of the anomaly. Then diagrams are included to illustrate the altered circulatory dynamics of the condition, reproductions of roentgenograms, and electrocardiograms. When indicated, supplementary information obtained from cardiac catheterization and from dye dilution studies are added. For many of the anomalies more than 1 specimen is pictured with a description of the clinical case. Throughout the book emphasis is on the particular pathologic specimen with the associated clinical story rather than emphasizing a statistic description of the particular anomally.

Appended are brief biographic sketches of important figures in the

(Continued on page 30A)



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(Continued from page 40)

field and a useful bibliography which covers the subject broadly if not completely.

The colored photographs which are featured throughout the book are of wax models rather than of the original specimens, while the original specimen is shown on the facing page in black and white photographs. The reader is thus impressed with the virtuosity of the model maker but often left with the thought that a colored photograph of the actual specimen might have been the best manner in which to demonstrate important anatomic detail.

F. John Lewis, M.D.

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The Microtomist's Formulary and Guide, by Peter Gray, Ph.D., 1954. New York: The Blakiston Co., Inc. $10.50.

The author has divided his book into two parts. The first part is a treatise on the art of making microscopic slides from biological specimens. The second part includes a classified list of the formulas and technics used in this art.

Many fine diagrams show the details of certain microscopic technics. Directions for preparing slides are clear and easy to follow.

The book is a fine reference and guide for the microscopist.

Craig W. Freeman, M.D.

•

Acute Anuria, by Claus Brun, 1954. Copenhagen: Ejnar Munksgaard. $4.50.

In the first part of the book the author reviews the history, morbid anatomy, pathogenesis of acute anuric renal failure, mechanism of anuria, and the functional pattern of the kidney.

The second part reports in detail his clinical investigations of 32 patients with acute renal failure and coexisting anuria or oliguria. He describes his technic in acquiring renal biopsy specimens which proved successful in about one-half of the attempts. The patho-anatomical changes are described. The glomeruli and vessels were always found to be histologically normal. The interstitial changes played a dominant part in the picture. The tubular changes were minimal in many cases and not specifically localized in the distal tubules (lower nephron). In some cases it was impossible to demonstrate any histologic changes.

The author concludes that renal ischemia and anoxia are the essential pathogenic factors in acute anuria.

Conservative treatment was successful in the majority of cases. Intermittent peritoneal dialysis is the best method and is accompanied by the least risk to remove metabolic waste products. Pulmonary edema is to be avoided.

Gordon W. Strom, M.D.

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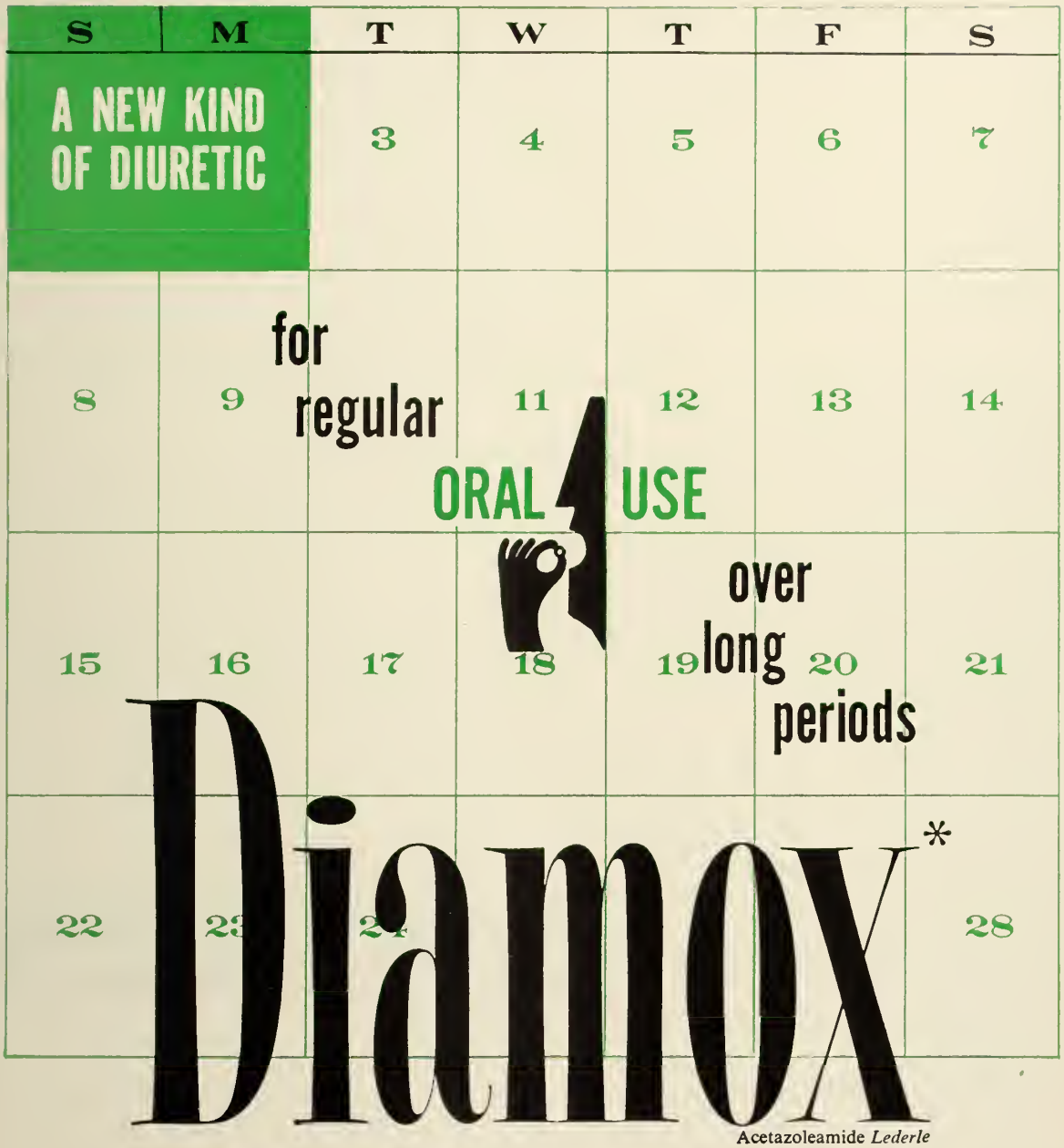
An Atlas of Pelvic Operations, by Langdon Parsons, M.D., and Howard Ulfelder, M.D. Illustrated by Mildred B. Codding, 1953. Philadelphia: W. B. Saunders Co. 231 pages. $18.

This book should be of tremendous value to all who are learning how to perform the several operations such as are used in gynecology. The book contains original drawings which show the many stages of the several operations. The only text is that which accompanies and explains the illustrations. The book is to be recommended.

Walter C. Alvarez, M.D.



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American College Health Association News . . .

The annual meeting of the Southwest section was held November 4 and 5, 1954 at Southern Methodist University. Approximately 35 people were in attendance. Officers elected for the coming year were: president, Lloyd Russell, Ed.D., Baylor University, Waco, Texas; vice-president, Evelyn Kappes, Baylor University, Waco, Texas; secretary-treasurer, Mrs. Lucille G. Steers, Texas Christian University, Forth Worth, Texas.

* * * *

The annual meeting of the North Central section took place at Luther College, Decorah, Iowa, October 22 and 23, 1954. There were 36 people present, representing the 5 states in the North Central section.

The nurses attending the meeting had a breakfast on October 23. Mrs. Mary Caron of Drake University, Des Moines, Iowa, was elected chairman of the group.

The following officers were elected for the next year: president, Dr. Donald Petersen, St. Olaf College, Northfield, Minnesota; president-elect, Dr. J. H. Gamet, Iowa State Teachers College, Cedar Falls, Iowa; secretary-treasurer, Anne Redman, Iowa State College, Ames, Iowa; executive committee member, Lillian Wilson, R.N., Carleton College, Northfield, Minnesota.

The next annual meeting of the North Central section will be held at Eau Claire State Teachers College, Eau Claire, Wisconsin.

Dr. Ronald Duffield has been appointed to the post of college physician at Wheaton College, Norton, Massachusetts. His new position became effective in October. In addition to his college service he will establish a private practice in Norton.

Dr. Duffield was born in England and holds the degrees of Bachelor of Medicine and Bachelor of Science from the University of London. He was house surgeon for a year at the Chelmsford and Essex Hospital in England, and for the past two years was on the staff of the Delaware Hospital in Wilmington, first as intern and then as resident in general practice. Dr. Duffield served in the Royal Air Force during World War II.

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Dr. Malcolm J. Chisholm has been appointed a staff physician of the Health Service at the University of Massachusetts at Amherst. The position became effective November 1.

* * * *

Dr. Edith M. Lindsay is on sabbatical leave from the University of California. She is at present conducting a study for the San Diego County Tuberculosis and Health Association of the San Diego community tuberculosis program.

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

Freedom and Progress for Minnesota's Handicapped Through Physical Rehabilitation

FRANK H. KRUSEN, M.D.

Rochester, Minnesota

THE GENERAL theme which has been selected for the exercises on dedication of this magnificent Mayo Memorial Building is "Medical Education and Research: Freedom and Progress in Mid-twentieth Century." This theme is a particularly happy selection to those of us who are interested in physical medicine and rehabilitation. In the twentieth century, development of this specialty underwent its greatest acceleration and, now, by mid-twentieth century, parallel advancement in practice, education, and research have placed it in a position to accept confidently the responsibilities cast upon it in the aftermath of war and pestilence.

It is well that this was so, for the promise of the good life made to the Gibson Girl had not been kept. Her children and her grandchildren had been under mutilating fire and the demand was almost overwhelming that adequate attention be given to physical, mental, social, and vocational rehabilitation. The freedoms of the handicapped citizen are not four but two; they are freedom from disability and freedom to progress toward opportunities equal to those of his able-bodied neighbor. Of these he must be assured and his rehabilitation can best be accomplished by group effort put forth by physicians and auxiliary health workers who again strive toward parallel development of practice, teaching, and research in the field of physical medicine and rehabilitation. When teams composed of physicians and their aids, working in adequately staffed institutions, have brought about maximum physical and mental rehabilitation, then social workers, educators, and other men of good will outside the walls must step in to assist in effecting the utmost in social and vocational adjustment of the disadvantaged and his environment, each to the other.

FRANK H. KRUSEN, *a 1921 graduate of Jefferson Medical College, is professor of physical medicine and rehabilitation in the Mayo Foundation and head of the section of physical medicine and rehabilitation at the Mayo Clinic.*

GROUP EFFORT

Dr. William J. Mayo and Dr. Charles H. Mayo, whom we honor today, are recognized as pioneers in the group practice of medicine. The institution which they founded at the turn of the century has been called "the embodiment of the individualism of a group of highly trained colleagues." [1]

The rehabilitation team of today bears the stencil of such group effort. A variety of specialists cooperatively render a high degree of unselfish devotion in the interests of the ill and disabled. The admirable physical medicine and rehabilitation unit which occupies the seventh

Read at the dedication ceremonies for the Mayo Memorial Building, University of Minnesota School of Medicine, Minneapolis, October 21, 1954.

and eighth floors of this Mayo Memorial Building could not have come into being without group effort. Many teachers in various fields have trained the personnel who will work in this unit and a variety of medical specialists collaborate in its activities.

Furthermore, a number of social agencies are assisting the unit in its work. The university is particularly indebted to Crippled Child Relief of Minnesota, which has furnished funds for equipment. The National Society for Crippled Children and Adults, the National Foundation for Infantile Paralysis, and other similar voluntary agencies have aided materially in developing the over-all program of the university in physical medicine and rehabilitation. Men such as Dr. Frederic Kottke and Dr. Miland Knapp have pioneered in the organization of this program. They, however, would be the first to declare, as I suggested earlier today, that physical rehabilitation must be supported by a number of other types of rehabilitation, to which internal medicine, psychiatry, and surgery contribute, and that all must be followed by social and vocational rehabilitation.

EDUCATION

The medical school of the University of Minnesota, under the leadership of Dean Harold Diehl, is in the forefront of the endeavor to educate physicians thoroughly in the field of physical medicine and rehabilitation. It was the first center in the country to offer, in 1936, three-year residencies in physical medicine. Now, as a result of this early effort, 52 different institutions[2] in the United States offer 146 residencies in physical medicine and rehabilitation. It is not by chance that, of the 47 chiefs of service listed as offering these residencies, 20 received all or part of their training here at the University of Minnesota. Not only has this medical school led the way in the training of physicians, but also it has explored in advance of most others in the training of auxiliary workers. I believe that the schools for physical therapists affiliated with this school have trained more experts in this field than any other medical school.

Education is not good education unless it is energized by the constant effort to develop and improve. The teachers of this unit have endeavored to follow the inspiring example of the Drs. Mayo, who were aptly called "communicative learners."[1] Dr. Will and Dr. Charlie traveled constantly and, in the course of their travels, learned new technics and new skills which they communicated to the hundreds of surgeons who came to watch them work.

Ever since I arrived in Minnesota, nearly two decades ago, while Dr. Will and Dr. Charlie lived, I have been impressed by the fast diffusion and long persistence of the ideals which they, with their peculiar aptitude in communicative teaching, instilled, directly or indirectly, unto the second and third generations of those who in some manner came under their influence: devotion to the service of mankind; dedication to the highest principles of medical care. These ideals have permeated the minds of all of their medical successors and have influenced all of the medical teachers at this institution. This new Mayo Memorial Building will serve to perpetuate their high ideals and, because I knew them, I know that they would have looked with favor on the teaching program here in the field of physical medicine and rehabilitation. It is a relatively new field and the two great brothers constantly sought to bring the good of the newest things in medicine and surgery to the people of this state.

RESEARCH

While adequate development of good teaching and constant improvement of medical practice are essential to the advance of any medical specialty, progress in education and practice remains slow unless the program of medical research is adequate. Dr. Alan Gregg,[3] of the Rockefeller Foundation, who will speak tonight at the dedication banquet, has said, "The word 'research' has a flavor of dissatisfaction with the search made hitherto, or with hitherto accepted explanations . . . research involves betimes a critical examination of our sources and ways of learning what we describe as facts." Facts must be re-examined regularly if teaching and practice are to advance satisfactorily.

This faculty, for instance, has been particularly aware of the precipitous incursion of the physical sciences into medical research. Physical medicine is concerned particularly with the applications of biophysics to medical practice. Early in its activities, the Baruch Committee on Physical Medicine and Rehabilitation sought the advice of a committee on research. Dr. Eugene Landis, the brilliant young physiologist at Harvard Medical School, was a member of this committee. He urged that the committee establish in various medical centers teams of investigators, such teams to be composed of laboratory scientists and clinicians. This wise counsel led to the establishment of many such teams in various medical schools throughout the nation. Usually a physiologist represented the laboratory and a physiatrist represented practice, and together

they formed the nucleus of a team. Usually, also, this nucleus was soon enlarged by the addition of biophysicists and biochemists on the laboratory side and by internists, psychiatrists, or surgeons on the clinical side. These teams of investigators have brought research in physical medicine and rehabilitation rapidly to the fore. One of the finest teams in the country is here in Minneapolis, where Dr. Maurice Visscher and his associates in the laboratory have collaborated effectively with Dr. Frederic Kottke and his associates in practice. Similarly, Drs. Edward Lambert, Julia Herrick, and Khalil Wakim in the laboratory have aided those of us who do the clinical research in the Mayo Foundation at Rochester. I desire especially to thank our laboratory colleagues in this medical school for their magnificent contributions to the development of sound research in physical medicine and rehabilitation. On the seventh and eighth floors of the Mayo Memorial Building is found not only space for clinical practice and for teaching but also laboratories for research.

MID-TWENTIETH CENTURY PRACTICE

It would be impossible to teach satisfactorily or to develop a good program in research unless such teaching and research were based firmly on good practice. The practice of physical medicine and rehabilitation has developed as it has by the middle of the century largely because of changing needs of patients, improved understanding of biophysics as applied to medicine, lessening of preoccupation with the treatment of acute illness, and increasing concern regarding management of chronic illness and serious disabilities.

Moreover, physicians in general have recognized shifts in the relative importance of diseases. During the first half of this century, many of the infectious diseases, including typhoid fever and the principal communicable diseases of childhood — measles, scarlet fever, whooping cough, and diphtheria — have been all but eliminated as causes of death. The death rate from tuberculosis has been diminished by about 90 per cent and the record for pneumonia is almost equally impressive.

In 1909, the life expectancy of the average American at birth was 46.3 years. By 1953 it had increased to 68.9 years. This is an increase of 22.6 years.[4] Achievements in longevity have necessitated the development of new approaches which will broaden and extend the physical treatment and rehabilitation of an ever-increasing number of chronically ill and seriously disabled persons. Now, as has been said, the physician's responsibility is not only to add years to life but also to add life to years. There are far worse things than death, and to save a patient from years of dependency may be much more humane than to save his life.

The new physical medicine and rehabilitation unit in the Mayo Memorial Building offers hope of freedom from dependency and of progress toward self-sufficiency for many of the disabled citizens of Minnesota. It will help medical students and graduate physicians to learn how to face their new medical responsibilities which are products of the shift in the relative importance of diseases. Voltaire was correct in his conclusion that the most powerful force that can be loosed in the world is an idea for which the time is ripe. And the time has come, to say it again, for promulgation of the idea that in the sixth decade of this century, freedom and progress for all requires that physicians, health workers, and others devoted to the welfare of mankind band together to provide adequate physical, mental, social, and vocational rehabilitation for handicapped, disabled, or chronically ill citizens.

The power of the idea that rehabilitation facilities must be expanded is evidenced by recent universal concern in that direction. The key program in physical medicine and rehabilitation instituted at the University of Minnesota is being copied all over the nation. We of this medical faculty must see that the program continues to serve as a model for others in their efforts to serve the ill.

The power of the idea that the handicapped must be rehabilitated is evident also in the actions of the federal government. Earlier this year President Eisenhower,[5] in his special message to Congress on the nation's health problems, said, "There are two million disabled persons who could be rehabilitated and thus returned to productive work. Only 60,000 now are being returned each year. Our goal should be 70,000 in 1955 . . . for 1956, 100,000. By 1959 with . . . states . . . sharing with the federal government, we should reach the goal of 200,000." In order to reach this goal of physical, mental, social, and vocational rehabilitation for 200,000 chronically ill or disabled persons a year, which has been set by President Eisenhower, and which has been supported by appropriate legislation, centers such as this one at the Mayo Memorial Building must perform almost a miracle of humanitarian endeavor and must perform it within the next five years. Even then, the object of rehabilitating each person who becomes ill or disabled will not have been attained

because, in addition to the great reservoir of disabled persons previously mentioned, it is estimated that each year some 250,000 persons become disabled by chronic illness or serious injury. Eventually, then, after the huge reservoir has been drained, there will be a quarter of a million persons each year who will still be in need of rehabilitation.

Therefore, facilities for hospitalization of the chronically ill, and for their rehabilitation in units such as this, must be expanded. Chronic disease accounts for 88 per cent of all patients who could benefit from rehabilitation. Casualties in war excluded, congenital conditions account for 2 per cent, occupational accidents and injuries for 5 per cent, and other accidents, including those in the home and on the highway, account for another 5 per cent, but disease supplies the full reservoir of incapacitation.[6]

FREEDOM AND SELF-DISCIPLINE

"Liberty exists in proportion to wholesome restraint," said Daniel Webster,[7] and, in my opinion, one of the greatest weaknesses of modern educational institutions is their failure to teach self-discipline. Attainment of freedom and progress for all in this dangerous atomic age requires increasing stress on the importance of self-discipline, not only among undergraduate students but also among our medical students. Bernard Baruch, who has given millions of dollars of his personal fortune for the advancement of physical medicine and rehabilitation and who has contributed generously to the program of this university, said recently, "The only freedom man can ever have is the freedom to discipline himself. That is what we are fighting for, to maintain our right to self-discipline instead of having the discipline of slavery and tyranny thrust upon us by a conquering enemy."[8] Baruch also quoted Woodrow Wilson as having said, "Liberty in itself is not government. In the wrong hands, in the hands of the unpracticed and undisciplined, it is incompatible with government."

Handicapped citizens likewise must be taught the disciplines which will help them to join with others in fighting for freedom and progress. Their efforts are needed if the social sciences are to begin to keep pace with the appalling progress of the physical sciences.

The example set by Dr. William J. Mayo and Dr. Charles H. Mayo, in their rigorous self-discipline and devotion to humanity, could lead toward advancement in social discipline which will permit survival of a free and progressive democratic nation. This Mayo Memorial Building, including its physical medicine and rehabilitation unit, undoubtedly will serve as a symbol of enlightened education and research and of the freedom and progress which is so devoutly sought. It is my hope that the achievements of the workers in this Mayo Memorial Building, guided by the enduring inspiration of Dr. Will and Dr. Charlie, will continue to expand and, notwithstanding present excellence, will prove to be but "the fair beginners of a nobler time." [9]

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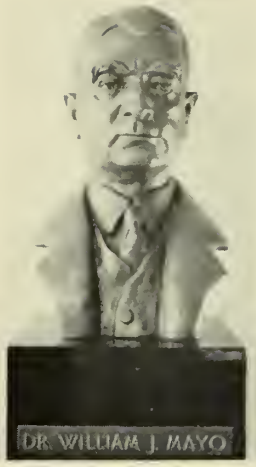
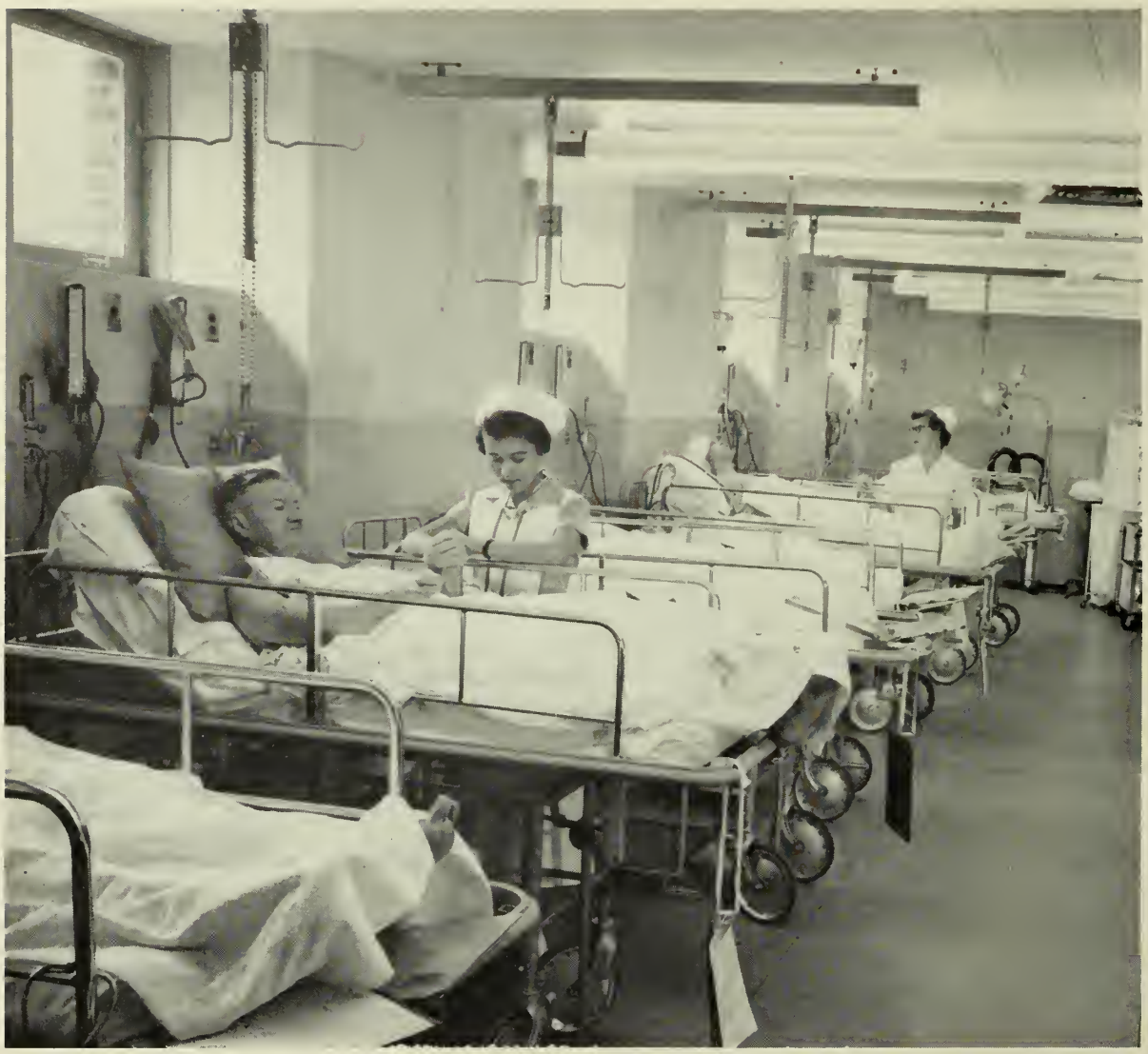
The MAYO MEMORIAL--A Picture Tour



FLANKING THE LOUNGE on either side are busts of Drs. Charles and William Mayo whose great contributions to medicine and the university are memorialized by this newest addition to the university medical school.

Raymond M. Amberg, director of University hospitals, is seen below relaxing in the beautifully appointed and spacious main lobby. Chair coverings in the lobby, some white and some orange, are of a plastic material similar to leather but washable, more durable, and less expensive than leather. Mrs. Donald Torbert, curator of design at Walker Art Institute, was interior decorator for the entire building. The colors, furniture, flooring, and draperies used throughout are a result of more than a year of planning.

THE MEMORIAL has 105 beds despite the fact that most of the building is devoted to diagnostic treatment and study facilities connected by seemingly endless stretches of corridor similar to the one on the right. Each of the 98 one-bed hospital rooms has an adjustable high-low bed, bedside cabinet, dresser, and each is equipped with an oxygen outlet. Most of the rooms have an adjoining bath and shower. When remodeling of the connecting old hospitals is complete, the combined hospital bed capacity will be 700. Below, Gertrude Gilman and Tomic T. Romson, assistant directors of University hospitals, inspect new furniture in one of the single rooms.



THE RECOVERY ROOM on the fourth floor and much of the equipment in it were especially designed under direction of Dr. F. H. Van Bergen, acting director of anesthesiology. Recessed control panels, overhead intravenous units, and special litters simplify the care of the patient as he comes out of anesthesia. Recovery of a dozen patients at one time can be observed under a lighting system which allows the detection of true skin color. In addition to the recovery room pictured, this floor also includes 14 air-conditioned operating rooms and a sub-central supply room.

THE SURGICAL DOMES provide a bird's-eye view of the operating theater. Students can observe an operation on the floor below and listen to the surgeons by means of a loudspeaker. Each observation dome has sufficient space to enable 16 persons to view an operation. There are 4 of these glass soundproof surgical domes located on the fifth floor. Viewers are in no danger of contaminating the sterile atmosphere of the operating room. The urology department, neurologic surgery rooms, and surgeons' conference rooms are also on the fifth floor. (Photo courtesy of the *Minneapolis Sunday Tribune*)

DR. IRVINE McQUARRIE, retiring head of pediatrics (left), and Dr. Robert A. Good, American Legion Heart Research professor, are shown above in the pediatrics conference room and library which was furnished by part of the McQuarrie Pediatrics Fund. Similar conference rooms are conveniently located for easy access for all of the departments housed in the Memorial.

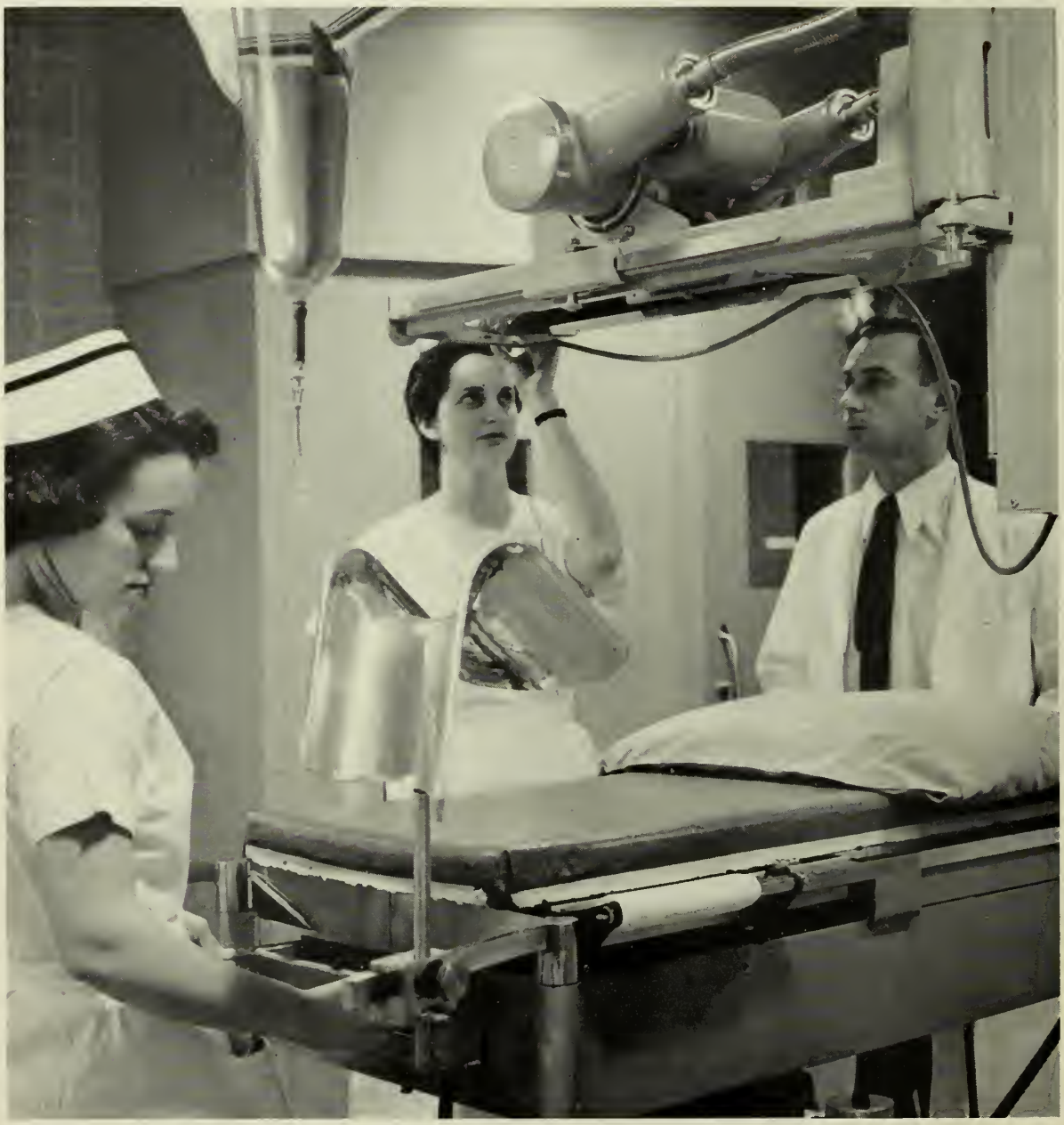
DR. CECIL J. WATSON (right) head of the department of medicine, makes the rounds of station 30, one of three medical stations, with junior clerks Robert Murray (left) and Jerome O'Hearn (center). New additional space devoted to the department of medicine, one of the largest academic medical departments of the university, makes possible the location of laboratories on the same floor as patient wards. This integration of the department permits more effective, time-saving work in both its main objectives—research and training.

Included in the department of medicine are divisions of internal medicine, dermatology, and clinical laboratory medicine. Training is offered for both undergraduate and graduate students. Courses in physical diagnosis and clinical laboratory medicine are given for sophomores and clinical training for juniors and seniors. The practical observation clinics are staffed primarily with part-time personnel, physicians with offices in St. Paul and Minenapolis who teach one or several days a week.

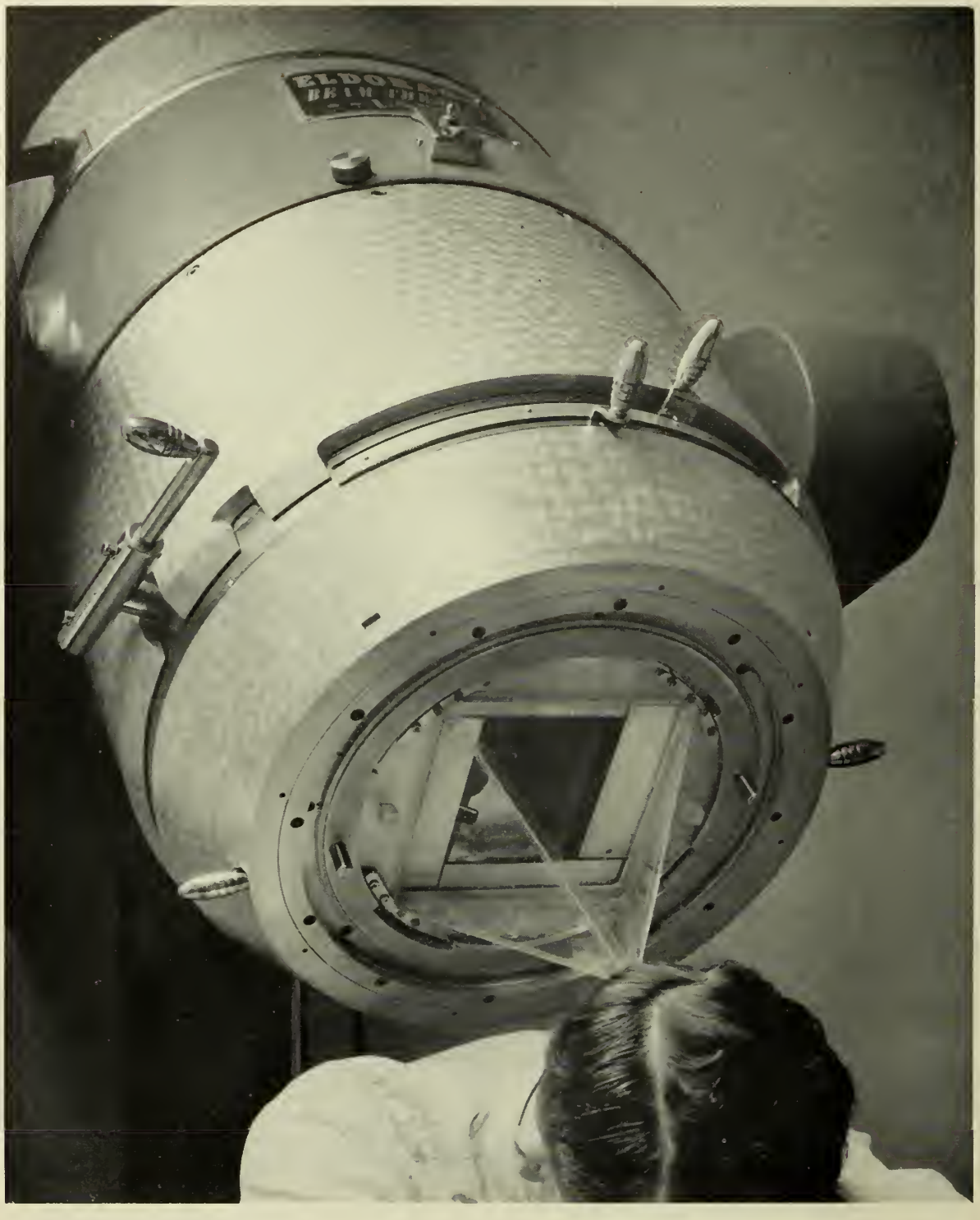
Research carried on by the department includes infectious diseases, heart diseases as well as liver and blood diseases, and diseases of the endocrine system.

THE NURSERY is surprisingly free from oxygen tank clutter because of a new piped oxygen system. The old-fashioned rocker still has a place, however, as the photo shows. In addition to the nursery, the hospital is continuing the boarding-in plan whereby mothers care for their babies in their rooms.

THE CYSTOSCOPIC TABLE and ceiling-mounted tube-stand x-ray which is part of the new equipment in 1 of the 4 cystoscopic rooms on the fifth floor is being examined by Dr. Milton Reiser, urology instructor. These rooms, 2 examining rooms with x-ray equipment, and dressing rooms comprise merely a part of the new completely consolidated urology department which is headed by Dr. C. D. Creevy.

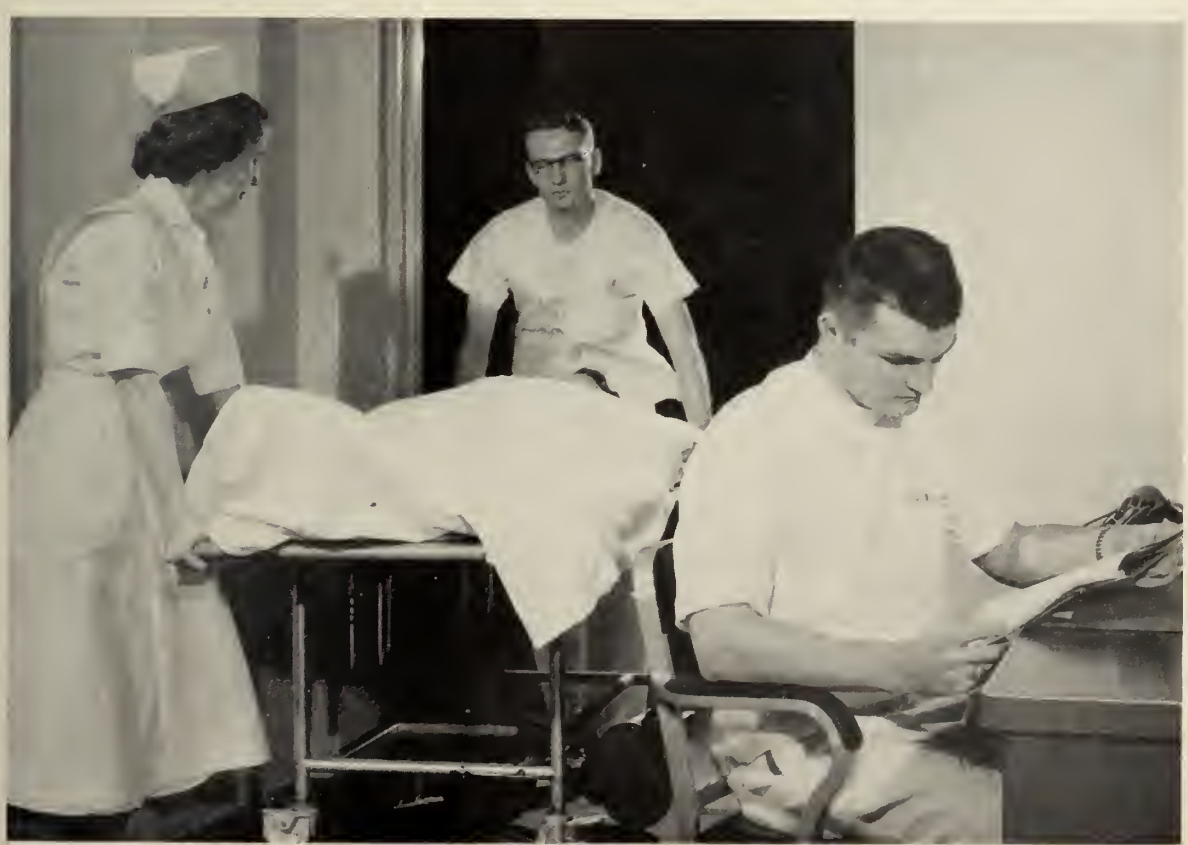


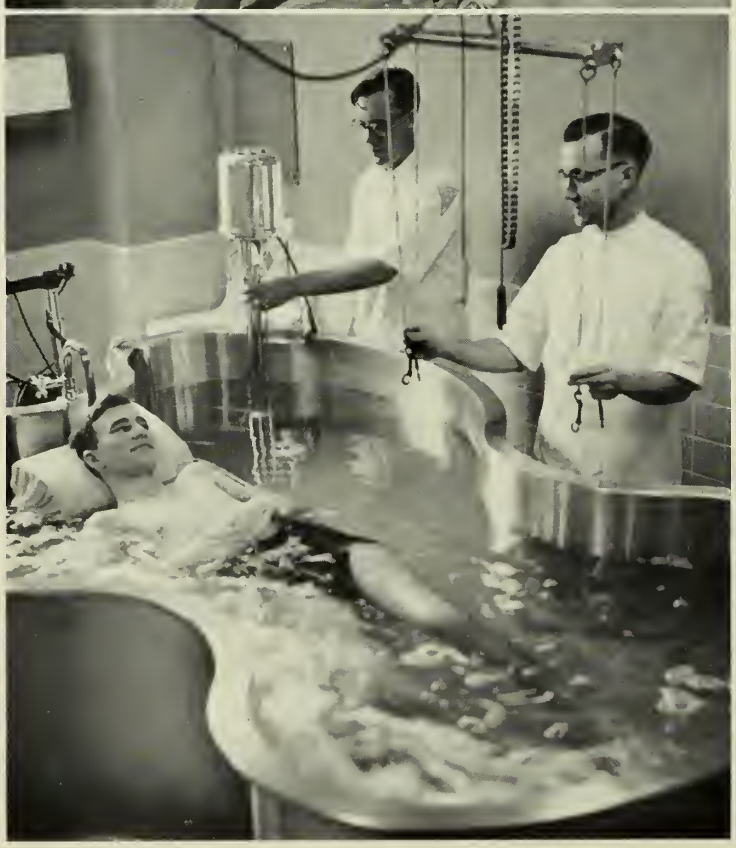
THIS NEW X-RAY UNIT which will rotate a patient to an angle of 90 degrees is in one of the university's 21 x-ray rooms. Automatic processing equipment will turn out 150 films per hour, size 14 x 17 inches. Such devices make possible the 150,000 films per year for the department's 50,000 examinations.



COBALT THERAPY of cancer patients is carried out in an especially constructed concrete underground room. Approximately 25 patients are now treated each day. The cobalt unit, one of the first of its kind in the country, was purchased in April 1953.

THE MAYO MEMORIAL AUDITORIUM, shown above, is on the third floor over the entrance to the 2-level garage which has a 200-automobile capacity. The 500-seat auditorium links Mayo Memorial and the hospitals to Owre hall and the medical science buildings. The garage entrance at ground level leads to the ambulance dock of the emergency room (below), which is staffed twenty-four hours a day by a nurse and intern.





THE PHYSICAL MEDICINE AND REHABILITATION department, headed by Dr. Frederic Kottke, occupies the seventh and eighth floors. Here handicapped persons are trained to adjust to their circumstances and taught to resume a life of useful independence.

Left: A 5-year-old girl with a spinal defect is strapped on a tilt board to become accustomed to an upright position. Physical therapist Sachiko Kaneko (right) and chief gymnasium therapist, Corrine Larson, are in attendance.

Bottom, left: An electric hoist enables therapists to lift a patient out of one of the new Hubbard tanks with little difficulty. The tank is shaped to allow room for a patient to exercise his arms and legs while immersed in water. Therapists in the picture are Bill Kasinkus and Rudy Ptak.

Bottom, right: Electric stimulation is used to test the condition of a patient's peroneal nerve. This diagnosis forms the basis of therapy by electric stimulation. Hazelle Erickson, physical supervisor and instructor, adjusts the current for Dr. Kottke.

RIGHT: DOGS, RABBITS, HAMSTERS, AND RATS are kept in new cages in the experimental animal quarters on the first and second floors. Dr. William G. Kubicek (right), professor of physical medicine and Dr. Alan P. Thal, research assistant in surgery, examine a rabbit which is being used in a pancreatitis experiment.

Bottom, right: Mrs. Agatha Eklund, head nurse, is opening 1 of the 3 different sized cyclomatic controlled autoclaves in the central supply room on the first floor. Oxygen, which is piped into the rooms throughout the new building, is controlled from this department. Other equipment includes a syringe washer, needle-cleaning machine, and glove-washing machine.

Bottom, left: Working with a new Warburg respirometer in a bacteriology laboratory on the tenth floor are Dolores Lauer, medical technologist; Dr. Herman Lichstein, associate professor of bacteriology and immunology; and Joseph Deal, graduate student. The equipment is used to study the metabolism of bacterial cells, particularly the way these cells produce and absorb gases.

THE PSYCHIATRIC LOUNGE on the sixth floor provides a comfortable place where patients may read, write, or watch television. Included among the facilities of the psychiatry department are 2 occupational therapy shops and an unlocked ward. With this additional space, the patient capacity of the department has been doubled.

DR. HAROLD S. DIEHL, dean of the college of medical sciences, in his office on the thirteenth floor. At the other end of this floor are the administrative offices of the School of Public Health. This school, one of the largest units housed in the building, also occupies the eleventh and twelfth floors.

A PANORAMIC VIEW of the Minneapolis skyline taken from the fourteenth floor.

Differentiation of Associated Cardiac Defects in Transposition of the Great Vessels

RAY C. ANDERSON, M.D., and PAUL ADAMS, JR., M.D.
Minneapolis, Minnesota

TRANSPOSITION of the great vessels constitutes one of the most severe, yet one of the most common types of congenital heart defects. Surgical treatment of this defect continues to be largely unsuccessful.[1,2]

Transposition of the great vessels may have a variety of associated cardiac defects. As better methods for the surgical alleviation or correction of the primary defect are developed, it will become increasingly more important to be able to diagnose the associated defects. The recent development of a controlled cross-circulation technic for intracardiac surgery at this hospital by Warden and associates[3] raises hope for a more successful surgical attack on transposition of the great vessels.

At the present time, clinicians are generally agreed that the associated defects[4] are practically impossible to identify. In her classical book on cardiac malformations, Taussig[5] has classified transposition of the great vessels according to the type of associated cardiac defect, and has described clinical pictures for them. However, except for the observation that patent ductus arteriosus may be suspected in the presence of differential cyanosis – hands darker than feet – no really specific diagnostic points are offered. Keith and associates[6] have published data relating to the clinical significance of murmurs in transposition of the great vessels. Thus, they reported that of 18 cases with an associated interventricular septal defect, 13 have had systolic murmurs, while of 26 without an interventricular septal defect, only 8 have had a systolic murmur. Of 14 without murmurs, only 2 have had an interventricular septal defect. Angiocardiography has been considered largely unsatisfactory for demonstrating associated defects,[6] and heart catheterization has been partially successful only in some of the cases already diagnosed as transposition of the great vessels by angiocardiography.[7]

We recently reviewed the clinical records of 32 autopsied cases of transposition of the great vessels at this hospital in an attempt to find some type of clinical or laboratory evidence that would help in the identification of associated defects. In pursuing this study, we have omitted cases involving single ventricle, partial transposition, pulmonary stenosis, or tricuspid valve abnormalities. The two features of diagnostic significance which became apparent were: the presence and intensity of murmurs, and the characteristics of the QRS complexes in the precordial electrocardiographic leads. Although descriptions of murmurs as reported by different examiners are difficult to compare, the cases reported have all been seen in the past three years, and the authors have personally examined almost all of these cases.

The cases are tabulated in table 1 according to the anatomic diagnosis, with the sex, intensity of murmur (all systolic), and electrocardiographic data listed in separate columns. In 5 cases, precordial leads had not been taken.

As can be readily seen from table 1, interventricular septal defects are frequently associated with loud murmurs (grade 3) and with an electrocardiogram showing the amplitude of the R wave in V_1 to be less than 75 per cent of the total RS amplitude. The presence of these two criteria identifies with fair accuracy those cases having an interventricular septal defect. The reverse situation, soft murmur (grade 2 or less) and the amplitude of R in V_1 approaching 100 per cent of the total RS amplitude, indicates the absence of such a defect. In none of 16 cases lacking an interventricular septal defect did the two criteria indicate such a defect, and in only 1 of 11 cases having an interventricular septal defect did the two criteria indicate instead its absence. When concordant, the two criteria indicate with a high degree of reliability the status of the interventricular septum. In a minority of cases, the criteria were discordant, with sometimes the murmur, sometimes the electrocardiographic sign being in error. Even if the diagnostic significance of these criteria is confirmed by further studies, their accuracy must be expected to be somewhat modified by the varia-

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

TABLE 1

Anatomic classification*	Sex	Murmur intensity	R/S V_1	R as % RS in V_1
Patent foramen ovale				
1. E. J.	M	2	15/0	100
2. M. G.	M	1	–	–
3. G. V.	M	1	15/0	100
4. B. P.	F	2	26/1	96
5. J. L.	M	2	25/0	100
6. L. A.	M	3	15/4	79
Patent foramen ovale, and patent ductus arteriosus				
1. C. O.	F	1	35/5	88
2. J. K.	M	2	5/8	38
3. E. M.	F	2	–	–
4. L. M.	M	2	17/0	100
5. C. D.	F	1	10/0	100
6. S. H.	F	0	15/0	100
7. B. W.	M	2	5/0	100
8. P. G.	F	0	–	–
9. L. N.	F	0	–	–
10. A. F.	M	2	30/24	56
11. S. N.	M	2	13/1	93
12. L. J.	F	1	14/2	88
13. S. U.	M	1	8/11, 6/0†	42, 100
14. S. M.	F	1	10/0	100
Patent foramen ovale, and interventricular septal defect				
1. B. G.	F	3	23/1	96
2. D. G.	M	3	10/10	50
3. T. H.	F	0	3/6	33
4. G. B.	M	2	4/5	44
5. G. D.	M	3	–	–
6. E. P.	M	3	9/11	45
7. D. G.	M	3	9/7	56
8. J. G.	M	3	15/21	42
Patent foramen ovale, patent ductus arteriosus, and interventricular septal defect				
1. A. O.	M	3	4/18	18
2. C. T.	M	2	12/11	52
3. S. C.	F	3	8/1	89
4. J. P.	M	2	15/0	100

*All cases have been assumed to have patent foramen ovales, and interatrial septal defects have been included with them.
†In this case, successive electrocardiograms differed in findings.

bility in size of septal defects. The only exception in the present series, J. P., involved an interventricular septal defect measuring only 6 mm. in size.

Another striking finding revealed by this table is the difference in sex incidence for associated patent ductus arteriosus. Thus, of 12 female cases of transposition of the great vessels, a defect which is far less common in the female than in the male, 9 involved a patent ductus arteriosus; of 20 male cases, only 9 had this as an associated defect. In other words, relative incidence of associated patent ductus arteriosus appears to be greater in the female sex, somewhat analagous to the sex incidence of uncomplicated patent ductus arteriosus.

In our clinical review, we have also encountered other signs which we consider helpful: (1) cases with pulmonary stenosis, as others have pointed out, usually have decreased pulmonary vascularity, and heart size remains smaller; (2) cases with only a patent foramen ovale or an interatrial septal defect may have normal pulmonary vascularity, mimicking cases with pulmonary stenosis and patent foramen ovale; and (3) in angiocardiographic studies, cases having a patent ductus arteriosus may show a "washed out" appearance of the descending aorta as compared to the aortic arch and carotid vessels.

SUMMARY

A review of the clinical data of 32 cases of transposition of the great vessels suggests that the presence of an associated interventricular septal defect may be highly suspected if the murmur is loud (grade 3) and if the amplitude of R in V_1 is less than 75 per cent of the total RS amplitude. In the female sex, relative incidence of associated patent ductus arteriosus appears to be higher.

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Cardiac Manifestations of Friedreich's Ataxia in Children

ROSALIND NOVICK, M.D., PAUL ADAMS, JR., M.D., AND RAY C. ANDERSON, M.D.

Minneapolis, Minnesota

Since the classical description by Friedreich in 1863,[1] the neurologic and cardiac manifestations of hereditary spinal ataxia have been carefully described by many investigators. The cardiac aspects of the disease, however, have received no mention in the American pediatric literature. The rapidly increasing interest in pediatric cardiology, and, more significantly, the availability of curative or palliative procedures for some of the congenital and rheumatic cardiac abnormalities make the problem of differential diagnosis ever more urgent and challenging.

Friedreich's ataxia is a recessive hereditary disease of the nervous system in which there is progressive demyelinization of the spinocerebellar tracts, the corticospinal tracts, and the posterior columns of the cord. As summarized by Ford,[2] the onset is insidious, the first symptom usually being a disturbance in gait. Ataxia of the arms and speech disturbances then appear. Examination in a well-advanced case reveals pronounced incoordination due both to cerebellar ataxia and to ataxia following degeneration of the posterior columns. Position and vibration sense are impaired. Deep tendon reflexes are lost. Plantar response may be extensor. Lateral nystagmus is seen. Scoliosis is almost always present, and the foot usually shows a very high arch with pes cavus and hammer toe deformities.

The cardiac abnormalities are an important aspect of the disease. Evans and Wright[3] evaluated the heart in 38 cases of Friedreich's disease. They reported that, although no patients had noticeable murmurs, enlargement of the heart on roentgenography was seen in 8 of the 38 cases, and abnormalities of the electrocardiogram were noted in 12 of 38 patients. A complete heart block with left bundle-branch block was observed in 1 patient. Electrocardiograms of 11 patients showed T waves which were flattened or inverted in the standard leads. The authors concluded that electrocardiographic changes are not related to age, sex, or onset of the disease. However, patients with abnormal electrocardiograms frequently have extensive involvement of the central nervous system.

More recently, Hejtmancik and associates,[4] Manning,[5] Flipse and associates,[6] Lorenz and associates,[7] and Schilero and associates[8] have all reported cases of Friedreich's ataxia in which cardiac abnormalities were present.

Although a few patients have cardiomegaly and cardiac symptoms, the most common evidence of myocardial pathology is inversion or flattening of the T waves in the limb leads and in the left precordial leads. The pathologic state from which the electrocardiographic changes stem has been carefully described by Russell.[9] In 3 autopsied cases of Friedreich's disease, she noted hypertrophy of the heart with small areas of fibrous thickening. Many fibers were undergoing fatty degeneration and scattered areas of fibrosis were seen. In 1 additional case, both ventricles showed extensive diffuse fibrosis. Small areas of necrosis were scattered throughout the myocardium. She concluded that the myocarditis of Friedreich's ataxia is of toxic origin. Nadas and associates[10] described a child in whom postmortem examination revealed extensive coronary artery disease and fibrosis of the left ventricle. They suggested that the myocardial changes may be secondary to abnormalities of coronary vessels.

In the past year, we have studied 5 children who showed cardiac manifestations of Friedreich's ataxia. Of these children, 3 were admitted for cardiac evaluation, neurologic manifestations being unrecognized in 2 and considered as unrelated in the other.

Case 1. M. H., a 15-year-old white female, was referred to the University of Minnesota hospitals for cardiac catheterization at the request of her physician, who thought she might have a congenital heart abnormality in addition to cerebellar ataxia. She had been a patient

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

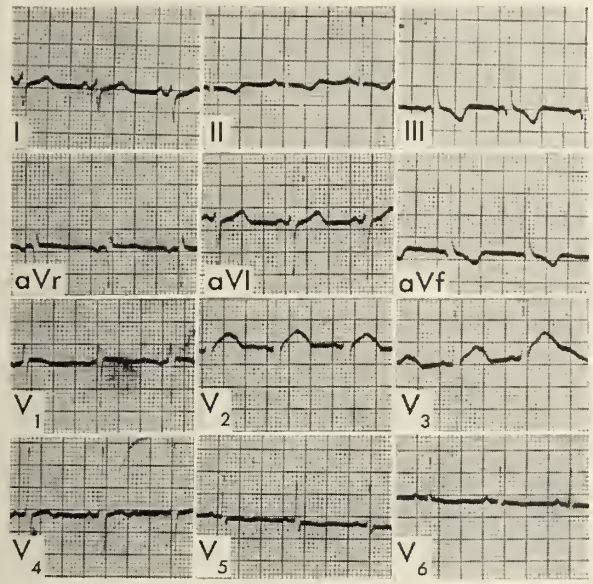


Fig. 1. Case 1. Electrocardiogram. Note negative T waves in leads II, aVf, and V_6.

at this hospital seven years before, at which time she gave a history of tremors and mild ataxia for two years. Significant physical findings at that time included a soft systolic murmur, choreiform movements, slurred speech, positive Romberg test, and bilateral absence of the knee jerk, ankle jerk, biceps jerk, and triceps jerk. Pes cavus deformities were noted. Chest roentgenography and an electrocardiogram were normal, as was the sedimentation rate. The patient was discharged with a diagnosis of rheumatic fever and chorea. For the next seven years she had very little difficulty. At 15 years of age she began to have a stumbling gait and to drop objects. She also complained of palpitations. No family history of neurologic disease was elicited other than a "slipped disk" in the father. Physical examination revealed a soft systolic murmur, poor coordination but no choreiform movements, a positive Romberg test, slurred speech, and nystagmus. Knee jerks, ankle jerks, biceps jerks, and triceps jerks were absent bilaterally. Vibration and position sense were impaired. Thoracic scoliosis was present as well as pes cavus. Roentgenography of the heart was within normal limits, but the electrocardiogram showed right axis deviation and negative T waves in leads II, aVf, and V_6 (figure 1). The presence of physical signs of cerebellar disease and of disease of the dorsal columns, of pes cavus, and of scoliosis, coupled with evidence of myocardial disease, established the diagnosis of Friedreich's ataxia.

Case 2. J. H., a 7-year-old white male, was referred to the University of Minnesota hospitals for cardiac evaluation. He had become ill a year earlier, at which time he was noted to have an elevated temperature for several days. His physician heard a heart murmur, and diagnosed rheumatic fever. He was kept on bed rest up to the time of referral. There was no family history of neurologic disorder. Physical examination on admission to this hospital revealed a rough systolic murmur at the third and fourth intercostal spaces, along the left sternal border. The child was grossly ataxic and had slurred speech. Nystagmus was present. Deep tendon reflexes were absent in both arms and legs. Mild scoliosis and pronounced bilateral pes cavus deformities were noted. Roentgenography of the heart revealed pronounced generalized enlargement but normal pulmonary vascular markings (figure 2). The electrocardiogram was abnormal, showing right axis deviation, right ventricular preponderance, and negative or biphasic T waves in all leads (figure 3). The typical findings of Friedreich's ataxia, that is, cerebellar ataxia with loss of deep tendon reflexes, scoliosis, and pes cavus, plus evidence of severe myocardial disease, were all clearly demonstrable in this patient.

Case 3. J. O., a 5-year-old white male, was referred to this hospital for investigation of an enlarged heart, discovered during an episode of virus pneumonia. There was no family history of neurologic disorder. The patient had no cardiac symptoms, but had been stumbling

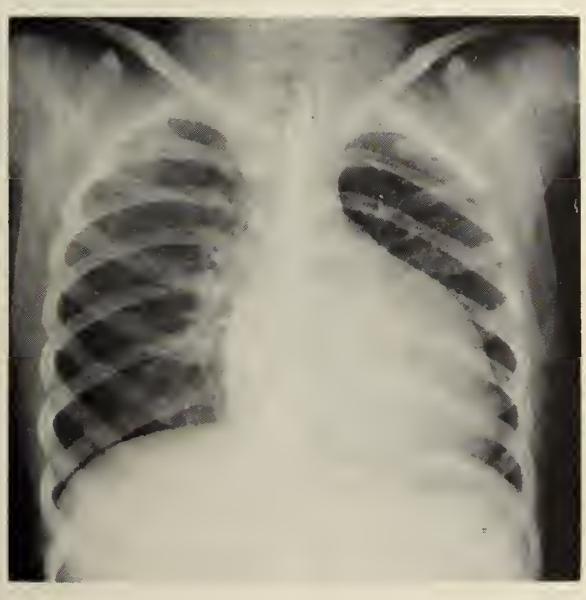
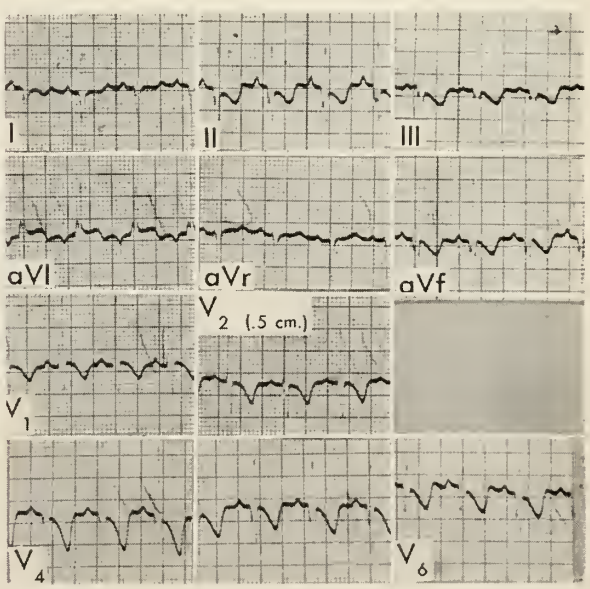
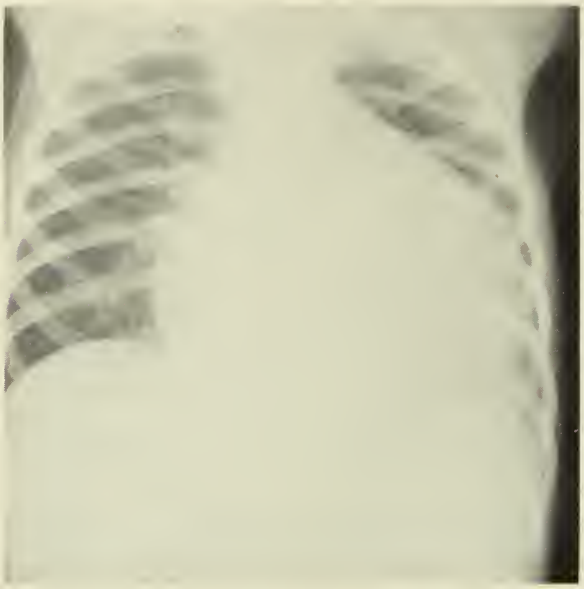


Fig. 2 *(left)*. Case 2. Roentgenogram of chest showing generalized enlargement of heart. Fig. 3 *(right)*. Electrocardiogram of same patient. Note negative T waves in all leads, especially leads II, aVf, and V_6.





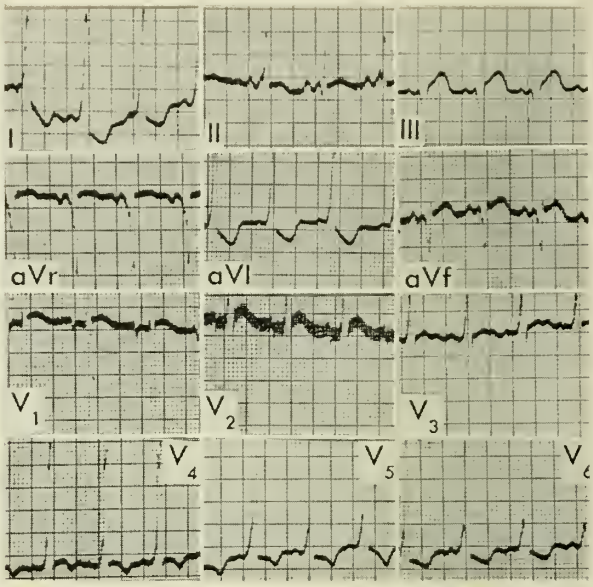


Fig. 4 *(left)*. Case 3. Roentgenogram of chest showing generalized enlargement of heart. Fig. 5 *(right)*. Electrocardiogram of same case. Note negative T waves in leads I, V_5, and V_6.

since the age of 3 years. Findings on physical examination included an ataxic gait, a positive Romberg test, absent deep tendon reflexes in both legs, and pes cavus deformities. Roentgenography of the heart revealed pronounced generalized enlargement (figure 4). The electrocardiogram was abnormal with negative T waves in leads I, V_5, and V_6 (figure 5).

Case 4. K. S., a 9-year-old white female, was referred to this hospital with a diagnosis of Friedreich's ataxia. She had had progressive difficulty in walking since 3 years of age. She had 1 sibling, case 5, with similar symptoms. Physical examination revealed a grossly ataxic child with extremely poor coordination. Her speech was explosive and scarcely intelligible. Deep tendon reflexes were absent in the legs and diminished in the arms. An extensor plantar reflex was present bilaterally. Vibration and position sense were diminished. Bilateral pes cavus deformities and thoracic scoliosis were present. No heart murmur was heard. Roentgenography of the chest revealed no cardiac enlargement. The electrocardiogram showed negative T waves in leads II, aVf, and V_6 (figure 6).

Case 5. J. S., a 6-year-old white male, was admitted to the hospital with his sister, K. S., with a diagnosis of Friedreich's ataxia. He had begun to have difficulty in walking at the age of 3 years. On physical examination he was moderately ataxic. Coordination was poor. All deep tendon reflexes were absent. Pes cavus deformities and mild scoliosis were present. A loud systolic murmur was heard at the left sternal border in the third and fourth left intercostal spaces. Roentgenography of the chest revealed no cardiac enlargement. The electrocardiogram showed inverted T waves in leads II, aVf, and a flattened T-wave in V_6 (figure 7).

It is of interest to note that in 3 of the 5 cases described, the patients were not suspected of having a neurologic disease when first referred, although the symptoms and signs of Friedreich's ataxia were clearly present. The cardiac abnormalities, which were fairly striking, were considered to be of rheumatic origin in 1 case, of congenital origin in another, and both congenital and rheumatic in a third case. The 2 patients in whom the neurologic manifestations of the disease were more striking, were, on the other hand, not suspected of having an associated myocarditis. Nadas and associates[10] emphasize the ease with which the myocarditis in Friedreich's ataxia may be confused with other forms of heart disease in children. In 1 of his cases an initial diagnosis of Sydenham's chorea was made, and in another, glycogen-storage disease. In 2 other

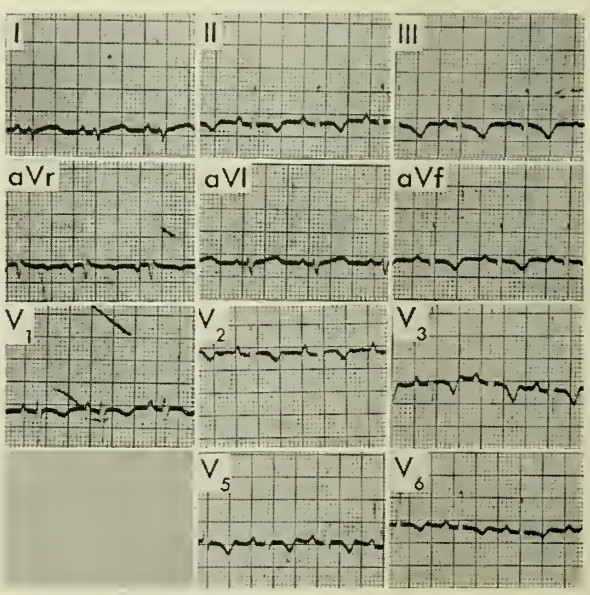


Fig. 6. Case 4. Electrocardiogram. Note negative T waves in leads II, aVf, and V_6.

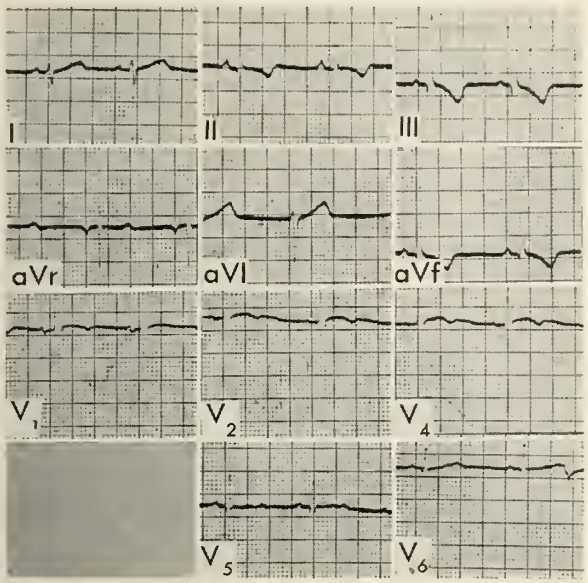


Fig. 7. Case 5. Electrocardiogram. Note negative T waves in leads III, aVf, and V_6.

cases, a cerebellar tumor was thought to be present, and the demonstration of the associated myocardial abnormality aided in establishing the correct diagnosis.

It is apparent then, in children with myocardial disease, consideration of Friedreich's ataxia in the differential diagnosis is obligatory. Similarly, in children with cerebellar ataxia, a search for evidence of myocardial involvement is equally urgent. As with any trait caused by a recessive gene, the disease can be expected to occur in siblings, but is rarely encountered in the parents or other relatives. A "negative family history" should, therefore, never be considered as evidence against the diagnosis of this disease. It should also be kept in mind that other types of hereditary neurologic disease, such as the muscular dystrophies and myotonia, may also have cardiac involvement.

SUMMARY

Descriptions of 5 children showing the cardiac features of Friedreich's ataxia are presented. The importance of considering Friedreich's ataxia in the differential diagnosis of myocardial disease in children is emphasized. The necessity of evaluating the cardiac status in children with neurologic disease is also stressed.

Addendum. Since the preparation of this paper, we have seen an additional case. This patient was an 8-year-old boy who had been treated for several years for foot deformities and gait disturbances. He was referred to us for evaluation of a recently discovered heart murmur and cardiomegaly. Findings were similar to those in the cases described in this paper, and were classical for Friedreich's ataxia.

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Coarctation of the Aorta in Infants

PAUL ADAMS, JR., M.D., MARJORIE KEELE, M.D., and IVAN BARONOFSKY, M.D.

Minneapolis, Minnesota

THE DIAGNOSIS of coarctation of the aorta in children and adults has been frequently discussed in recent years since this defect can now be corrected by surgery. The diagnosis and treatment of this malformation in infants, however, has received less attention because of the feeling among pediatricians and surgeons that the operation can only be successful if performed at an older age. A second factor in deferring operation has been the feeling that infants with symptoms of heart failure from coarctation of the aorta must have associated lesions or long hypoplastic segments of aorta and were, therefore, not amenable to surgery. Fortunately, this diagnosis often can be made by clinical observation, and a high percentage of these patients have defects that can be corrected by present surgical technics. Unfortunately, a high percentage of infants born with this malformation will not survive beyond infancy to reach the optimum age for surgery. Calodney[1] has emphasized this in his report of 22 infants, 18 of whom died during the first eight weeks of life. Of the remaining 4 patients, 1 died at 67 days, 2 died at 4 months, and 1 died at 20 months of age. Bahn and associates[2] reported 3 patients who died in infancy from heart failure secondary to the closing of the ductus arteriosus. Rogers and associates[3] reported 2 cases in infancy with death due to left ventricular failure. Our impression is that this type of experience is not uncommon among practicing pediatricians. Solomon and King,[4] on the other hand, reported 2 cases in infancy that were tided over by medical management in spite of recurrent heart failure. Gross[5] also mentioned 8 cases with signs of heart failure in infancy. He stated that 2 of these infants died and that 6 were tided over by medical management until they regained cardiac compensation. Ziegler[6] reported 57 cases of coarctation in infancy with 15 deaths or a 38 per cent mortality. When left ventricular hypertrophy or left bundle-branch block was seen on the electrocardiogram, the mortality was 60 per cent in early infancy. Reports of successful surgical treatment in this age group appear to be very limited. Kirklin and associates[7] reported a successful result on a 10-week-old infant. Ziegler[6] mentioned 1 patient operated on successfully at 5 months. We reported 2 infants who were successfully operated on under 6 weeks of age.[8] These patients are included in this report.

The purpose of this report is to re-emphasize that coarctation of the aorta may be diagnosed clinically during infancy, that it is probably the most common cause of heart failure in this age group, and that it may be successfully treated by surgical technics now available. The 8 patients to be presented were under 1 year of age. Their diagnosis was coarctation of the aorta and surgical treatment was undertaken because of cardiomegaly and recurrent or uncontrollable cardiac decompensation. These patients were seen at the University of Minnesota hospitals in the three-year period 1951 through 1953. There were 2 deaths and 6 survivals.

ANALYSIS OF CLINICAL SYNDROME

These 8 patients had similar histories and physical findings and will be presented as a composite picture. There were 5 males and 3 females. The first symptoms began a few days after a normal pregnancy and delivery. The usual finding was failure to nurse well. Differential cyanosis was noted in the legs on only 1 patient, and this gradually cleared and was not seen on any of the patients at the time of admission. Rapid respirations, intermittent cyanosis, and an enlarged heart had been noticed by the referring physician in most cases. Definite signs of heart failure requiring digitalis had been recognized in 3 patients before referral. Heart failure was definitely diagnosed in 2 others on admission and may have been present in all but 1 patient prior to surgery.

At the time of admission, the ages ranged from 12 days to 11 months. The blood pressure

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

in the arms was elevated over the legs in all instances – varying from 100 mm. Hg systolic to 170 mm. Hg – average of 125 systolic. These pressures were usually taken by the "flush" method. Blood pressures in the legs were not obtainable by auscultation but by the "flush" method; the average was 73 mm. Hg systolic. No cyanosis was noted in any patient. A systolic murmur was heard in 6 patients and was absent in 2 patients. There were no distinguishing features about the murmur that were helpful in the specific diagnosis. The femoral arteries were palpable in only 1 patient. The liver was considered abnormally palpable in only 2 patients.

The electrocardiograms showed right axis deviation in 6 patients and normal axis in 2 patients. Precordial leads were available in 6 patients. Of these patients, 2 showed right ventricular hypertrophy only. Right ventricular hypertrophy along with negative T waves in $V_{4\text{-}6}$, suggestive of left ventricular strain or digitalis effect, was found in 2 patients. Evidence of left ventricular preponderance appeared in only 1 patient. There was no evidence of ventricular hypertrophy in 1 patient. The 1 patient showing only left ventricular preponderance expired at the completion of surgery and was shown at autopsy to have endocardial fibrosis in addition to coarctation.

ROENTGEN FINDINGS

All patients had markedly enlarged hearts. In 2 of the patients cardiac enlargement was massive (figures 1 and 2). The enlargement was usually generalized so that both left and right ventricular hypertrophy were noted. The left atrium was noticeably enlarged in every patient. The pulmonary vascular markings were exaggerated in every patient except the 2 whose cardiac shadow was so large that these markings could not be separated.

SPECIAL STUDIES

Heart catheterization was performed on 2 patients because we suspected the presence of associated intracardiac anomalies. There was no definite evidence of left to right shunt in either patient. The pulmonary artery pressure was at the upper limits of normal in both patients. Retrograde aortograms were done on 2 patients. We feel that this is not necessary in the ordinary case. In 1 patient in whom this was done the femoral arteries were palpable although the blood pressure was 110 in the arms and 70 mm. Hg systolic in the legs. The murmur suggested a patent ductus arteriosus. The retrograde showed the patent ductus and a mild coarctation; this was confirmed at surgery. This case differed from the other 7 reported in that the

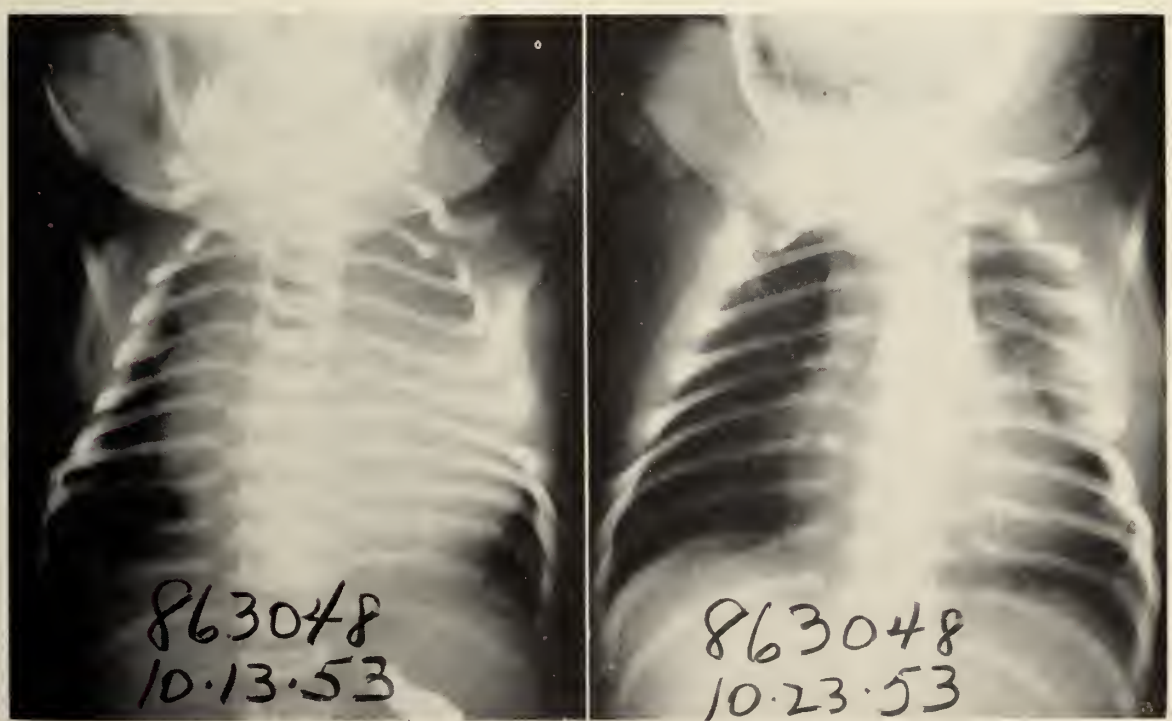

Fig. 1 *(left)*. Chest film of 2-week-old infant with coarctation of the aorta and widely patent ductus arteriosus before surgery. Note pronounced cardiomegaly. Fig. 2 *(right)*. Chest film of same infant ten days after operation. Note pronounced decrease in heart size.

patent ductus arteriosus was the predominant lesion.

A simultaneous flush method for taking blood pressure is a simple procedure which we have found valuable as an aid to diagnosis. It consists of joining 2 infant blood pressure cuffs together with a Y tube and wrapping 1 on the arm and 1 on the leg. After the patient's arm and leg have been blanched by pressure, the cuffs are inflated simultaneously to a pressure above the systolic. As the pressure is then gradually lowered, the hand is seen to flush at a higher pressure and sooner than the leg. This method occurred to us as a result of several erroneous blood pressure values obtained when an infant was crying and uncooperative. If the infant cried when arm pressure was taken and was quiet when leg pressure was taken, a false impression of coarctation of the aorta resulted.

RESULTS OF SURGERY

Successful end-to-end anastomosis was accomplished in each instance. The narrowed or hypoplastic proximal segment was never such that this could not be accomplished adequately. A more detailed report of 2 of the youngest patients has been submitted by the authors in another publication.[8] An excess of bleeding and collateral vessels was noted in only 1 patient, 5 patients were noted at surgery to have diminished or absent collaterization. The ductus arteriosus was very large in 2 patients. Both had tremendous cardiomegaly and developed difficulties referable to the cardiovascular system at the youngest age, namely, 12 to 13 days. The ductus was small or completely closed in 5 patients. The insertion of the ductus relative to the coarctation could not always be determined accurately at the time of surgery or from the excised specimen, but was usually stated to enter right at the site of coarctation.

Shortly after completion of the operation, 2 of the patients died. Of these, 1 patient, 11 months old, had endocardiac fibrosis of the left ventricle in addition to the coarctation, but had no other defects. The other patient had an associated interventricular defect. Of the 6 surviving patients, the femoral arteries are palpable in all but 1, and this patient still has blood pressures of 110 systolic in the arms and 90 systolic in the legs and is asymptomatic. The patients have been followed from two months to two years, and all are doing well. Persistent murmurs suggestive of interventricular defects are present in 3 of the patients. Figure 2 illustrates the rapid decrease in heart size after surgery in the same patient as shown in figure 1.

DISCUSSION

Our experience tends to agree with reports of Calodney and Carson[1] and Bahn and associates[2] that "infantile" coarctation of the aorta, or coarctation of the aorta in infancy, may produce death from heart failure and yet be an isolated, surgically amenable lesion. Taussig[9] has stated that when other grave anomalies are associated with coarctation, such as transposition of the great vessels or mitral atresia, the signs of coarctation may be completely masked. Jacobsen and associates[10] have pointed out that coarctation combined with aortic stenosis failed to produce the expected hypertension in the arms, although a distinct differential in blood pressures was found to exist between the arms and legs. Our experience agrees with this and we feel that a necessary criteria of operability by present technics is the existence of hypertension, over 100 mm. Hg in infants, in the upper extremities. During the period covered by this report, 1951-1953, we have seen only 1 case of uncomplicated coarctation of the aorta in whom hypertension was not present in the arms. This patient was not diagnosed or operated on antemortem and, therefore, was not included in this report. In this case the narrowed segment was long and included the take-off of both subclavian vessels. At present this form which occurs infrequently must still be considered inoperable. Subaortic stenosis or mitral stenosis and/or interventricular septal defect may soon become operable by the technic of open cardiotomy using controlled cross circulation as reported by Warden and associates.[11]

The advisability of performing surgery at an early age of a few weeks has been questioned. Gross[5] states that he postpones operation on all his patients and that the large majority may be tided over by medical management. Our experience and that of Calodney and Carson[1] has been exceptionally poor after the patient has gone into heart failure. Recurrent failure is inevitable and often uncontrollable. However, we have recently seen 2 children with coarctation of the aorta who have survived heart failure occurring in infancy. These patients were 12 and 3½ years of age. Physiologic studies on the 12-year-old girl revealed a pulmonary artery pressure of 100/70 mm. Hg. The catheter passed through the patent ductus arteriosus which entered into the descending aorta beyond the coarctation. The pressure in the descending aorta was 80/70 mm. Hg. The oxygen saturation in the descending aorta was only 81 per cent, indicating the existence of a right to left shunt. The brachial artery had an

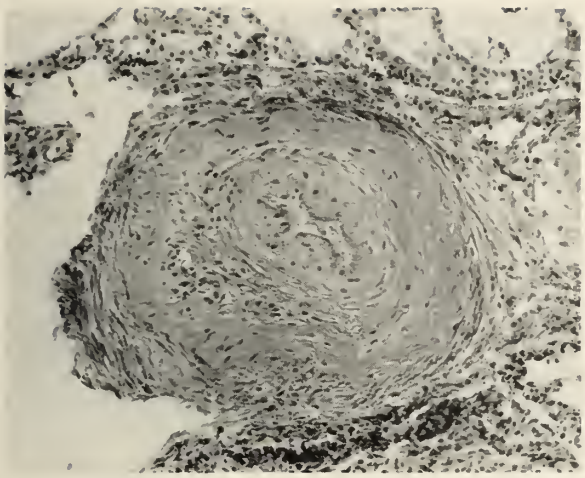

Fig. 3. Pulmonary arteriole from patient with coarctation of the aorta and patent ductus arteriosus entering the aorta distal to the coarctation. Here is pronounced obliteration of the lumen of the vessel associated with elevated pulmonary pressure.

oxygen saturation of 87 per cent suggesting desaturation secondary to pulmonary pathology. She was operated on for the coarctation. As the patent ductus was clamped the heart stopped and the patient expired. The changes in the lungs were of special interest (figure 3). The lumena of the small vessels were nearly occluded by the dense medial and intimal thickening. These changes have been described in detail by Edwards and associates[12] in 4 such patients.

The second patient aged 3½ years gave a history of hospitalization for the first 30 days of life with rapid respirations, cyanosis, and enlarged heart. He gradually improved but had had considerable difficulty all his life. He was digitalized at 2½ years of age for heart failure. He was catheterized at the age of 3½ years. No evidence of left to right shunt was found, but the pulmonary artery pressure varied between 64 mm. Hg to 84 mm. Hg systolic. A complete aortic block was resected at surgery and the patient survived. Unfortunately no lung biopsy was taken but it seems safe to postulate that pulmonary arterial changes had already occurred similar to those present in the 12-year-old patient just illustrated. With these cases in mind, 3 cases of coarctation of the aorta who had died at 4 weeks, 12 weeks, and 1 year were reviewed. The pulmonary changes of the small vessels may have been slightly more exaggerated than in normals of the same age. Any difference, if present, was such that correction of the basic lesion would have been expected to permit the normal differentiation into adult type of pulmonary arterial histology. We feel, therefore, that surgery is indicated in coarctation of the aorta in infancy after heart failure has occurred. If the patient can be safely guided through infancy by medical management, surgery may be deferred a short while, but deferral until age 4 to 5 years is probably longer than is physiologically safe.

SUMMARY

1. Studies of 8 patients with coarctation of the aorta operated upon during infancy are presented. Of these, 6 survived the operation and all had good results.

2. Indications for operation included recurrent or uncontrollable heart failure, cardiomegaly, and hypertension in the upper extremities indicated by blood pressure over 100 mm. of Hg.

3. Because of the observation that pulmonary vascular changes progress, it is suggested that a long deferment of surgery may be hazardous.

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The Nature and Management of Acute Renal Failure*

HOWARD M. ODEL, M.D.

Rochester, Minnesota

The broad problem of acute renal failure is germane to almost every specialty in the field of medicine. Indeed, probably all clinicians, regardless of whether they are specialists or general practitioners, at some time in their professional careers have been confronted with sudden urinary failure in a patient, who, in all probability, was ill from some cause, extrarenal in origin. The multiple and complex problems of diagnosis and therapy in the management of such a complication have few counterparts in the practice of medicine. This is not difficult to understand when the numerous situations under which such a complication may arise and the varied functions of the kidney are considered. This organ is charged with elimination of nitrogenous and other end products of metabolism, with conservation of threshold and other substances necessary to the organism, with regulation of acid-base balance, with conservation of water, and with some other complex, and, at present, poorly understood functions.

A hopeless prognosis usually is meted out to the patient with renal failure and uremia, because these conditions occur most frequently as terminal events in the course of advanced chronic parenchymal renal disease, such as chronic glomerulonephritis, pyelonephritis, the late stage of hypertensive cardiorenal disease, and other diseases. However, acute renal failure with suppression of urine and consequent uremia is often a complication of surgical and nonsurgical situations and may be wholly reversible. Yet a high mortality rate is one of the outstanding features of the syndrome. However, early recognition of acute renal failure, understanding of its nature and clinical course, and the prompt institution of intelligent management may be rewarded with an eventual return of renal function to a normal or nearly normal state and recovery of the patient.

HOWARD M. ODEL, *a 1933 graduate of Northwestern University, is associate professor of medicine in the Mayo Foundation and consultant, section of medicine at the Mayo Clinic.*

The mechanism of acute urinary suppression in the various situations under which it occurs is not wholly nor clearly understood at present, nor have the many therapeutic measures and agents recommended for its treatment enjoyed universal acceptance. Rather than enter a long and detailed discussion of the many theories relative to pathogenesis, I propose to consider the clinical nature of the condition briefly and then some of the therapeutic measures, emphasizing the necessity of constant and meticulous study and care of a patient suffering from acute renal failure.

NATURE OF ACUTE RENAL FAILURE

In the past few years, the syndrome associated with acute failure of the kidneys to excrete urine has been given various designations: "the renal-anoxia state,"[1] "lower nephron nephrosis,"[2] "hemoglobinuric nephrosis,"[3,4] and "acute tubular insufficiency." A partial list of the causes is given in table 1. Regardless of causative background, the renal lesions usually appear similar histologically. However, in a few cases in which the cause of death is uremia secondary to acute renal failure, histologic study of the kidneys at necropsy fails to offer an adequate morphologic explanation of the failure of the kidney to form urine.

The clinical picture, however, is almost invariably the same, regardless of the etiologic factor. The onset is sudden; oliguria or anuria develops in most cases within a few hours after the provoking situation has occurred, although in exceptional cases suppression of urine may be delayed for several days. Retention of nitrogen and other metabolic waste products in the blood soon occurs. Concentrations of urea, nonprotein nitrogen, creatinine, inorganic sulfate, and phosphate in the blood may become astoundingly high in a short time. In some cases the concentration of urea in the blood may exceed 200 mg. per 100 cc. in forty-eight to seventy-two hours,

*Read at the meeting of the North Dakota State Medical Association, Grand Forks, North Dakota, May 1 to 4, 1954.

TABLE 1

SOME CONDITIONS IN WHICH ACUTE (REVERSIBLE) RENAL FAILURE MAY OCCUR

SHOCK	
Anoxia	Hemorrhage, concealed postpartum
Abortion	Shock, however caused
Carbon monoxide poisoning	Uteroplacental damage
Gunshot wounds	Vascular injury
Head injuries	
DISTURBANCES IN ELECTROLYTE BALANCE	
Acidosis	Diabetic coma
Addison's disease	Hematemesis
Alkalosis	Hypochloremia
Anemia, pernicious	Intestinal obstruction
Cholera and diarrheas of other cause	Pneumonia
	Pyloric stenosis
	Vomiting, excessive
PIGMENT EXCRETION	
Blackwater fever	Incompatible blood transfusion
Burns	Nontraumatic muscular ischemia
Crush injury	Yellow fever
Heat stroke	Weil's disease
Icterus neonatorum	
ALLERGY	
Eclampsia	Meningococcal toxin
Favism	Serum sickness
Incompatible blood transfusion	Sulfonamide sensitivity
	Typhus fever
CHEMICALS	
Alloxan	Mushroom and other organic poisons
Bichromate	Oxalate
Bismuth	Phosphorus
Bite of the black widow spider	Tartrate
Carbon tetrachloride	Tetrathionate
Cresol	Uranium
Mercury	Uric acid

whereas, in other cases such concentrations may not be reached for several additional days. Patients in whose blood metabolites accumulate slowly appear to withstand anuria more comfortably than those in whose blood the accumulation is more rapid. Indeed, healing of the renal lesion, with resumption of urinary formation, seems more prone to occur in cases in which azotemia and uremia develop slowly. If suppression of urine lasts for several days and the concentration of metabolites in the blood becomes sufficiently great, uremia may supervene with its characteristic train of symptoms and signs, confusion, restlessness, headache, nausea, vomiting, convulsive seizures, and ultimately coma. Slight or moderate elevation in blood pressure is the rule in acute renal failure, but the blood pressure almost never reaches levels characteristic of essential hypertension, or of hypertension secondary to advanced chronic renal disease.

Complications are likely to be conspicuous. Acute congestive cardiac failure may occur and may increase the complexity of the situation. Peripheral or pulmonary edema may develop as a result of congestive heart failure or of administration of excessive amounts of fluid. Hypoproteinemia is rarely the cause. The concentration of plasma proteins in the presence of acute renal failure may be below normal, but rarely are the plasma proteins decreased to a level sufficient to produce edema. Hypochloremia and hyponatremia are almost invariably present to some degree and are due in some instances to loss of chloride through vomiting, a frequent symptom. However, decrease in the levels of chloride and sodium in the blood may occur without exogenous losses, possibly as a result of redistribution of these ions.

Frequently, potassium intoxication enters the clinical picture of acute renal failure. It is secondary to impaired excretion of potassium[5,6] and excess protein catabolism which results in cellular breakdown and release of potassium into the extracellular fluid. In fact, the patient may die from the deleterious effects on myocardial function of excessive amounts of potassium in the circulating blood.

Duration of the period of oliguria or anuria is variable, depending largely on the extent and severity of the renal lesion and on the nature of the causative factor. Some degree of renal excretory function may be resumed as early as three or four days after the initial insult, or it may be delayed for seven to ten days or longer. Patients whose uremic symptoms develop slowly may remain in relatively good health during the anuric period, whereas other patients whose uremic symptoms develop rapidly may die before clinical evidence of healing has become manifest. With formation of urine reestablished, the daily volume of urine increases gradually and, within a short time, striking diuresis usually occurs. As a rule, for several days after the onset of diuresis, concentrations of urea and other nitrogenous constituents of the blood continue to rise. Frequently a decrease in concentration of blood urea lags behind the onset of diuresis by as much as five to seven days. This should not be cause for alarm when the clinical status of the patient is good otherwise, but it may represent continuing morbidity for a patient whose situation is critical in spite of return of urinary flow. However, when the concentration of blood urea begins to decrease, diminution of the concentration of this and of other waste products

in the blood may be rapid. During the postanuric period, with exeretion of relatively large volumes of water incident to the so-called washing out of nitrogenous and other waste produets, rather dramatic improvement in the patient's clinieal eondition is noticed.

TREATMENT: GENERAL CONSIDERATIONS

That aeute renal failure often is a self-limited, reversible disease, and that the reparative power of the kidney is great are extremely important eoncepts to be borne in mind when approaching the problem of treatment. In many cases the condition is relatively mild and patients may recover if treated conservatively. Administration of exeessive quantities of sodium salts and fluid may lead to peripheral or pulmonary edema, with ultimate death. Conversely, the lives of some patients who are severely ill may be saved if derangement in the electrolytes and body fluids associated with anuria and uremia can be prevented. Some clinicians have voiced the opinion that much of the high mortality rate among patients with acute renal failure can be explained on the basis of the type of management provided and that more conservative treatment, based on correction of primary abnormalities in eleetrolyte and fluid balance, may result in an increase in the recovery rate.

The clinical problems differ in each case; hence, individual treatment of eaeh patient is essential. In order to attain the highest degree of success, careful clinical appraisal of the patient's condition during the period of acute suppression of urine is of paramount importanee. The state of nutrition, eireulation, and the fluid requirements of the patient should be evaluated daily. This involves eareful recording of the intake of fluid, both by the oral and the parenteral route, and of all fluid lost from the body. The concentrations of urea (or nonprotein nitrogen) and chloride, and the carbon dioxide-combining power of the blood should be determined daily also, because in the presence of uremia, these values may fluctuate widely from day to day. It has been my practice to determine on alternate days the value for hemoglobin, the erythrocyte eount, and the concentration of protein in the plasma. Moderate to severe seeondary ancmia may develop in the eourse of acute renal failure, probably due to toxic depression of bone marrow activity and also apparently to inerease the destruction of erythrocytes. Plasma proteins may become depleted, partly on the basis of the anemia and partly because of decreased intake of protein.

Therapeutic objectives in aeute renal failure should be eonsidered in 3 categories: (1) early treatment, (2) maintenanee during the period of oliguria or anuria, and (3) management during the postanuric period or the period of diuresis. Muirhead and Hill[7] have considered these 3 objeetives in a slightly different way. They have divided acute renal failure into 3 stages, namely, the phase of renal damage, the phase of renal insufficiency, and the phase of diuresis.

EARLY TREATMENT (PHASE OF RENAL DAMAGE)

The treatment of acute suppression of urine should be eonservative. If any manifestations of eireulatory failure exist, appropriate measures to correet it should be instituted. Otherwise, therapy, for the most part, is limited to maintaining the patient in as near normal metabolie balance as possible until the kidneys have an opportunity to effect anatomie and funetional recovery. Anuria or oliguria usually invokes in the physieian an urge to do something drastie in order to open up the kidney. Procedures, ranging from the use of numerous vasodilating agents to the use of various diuretic agents and even surgieal measures, sueh as renal decapsulation, have been employed. The value of such measures is by no means established. Their use has not been justified in many instances, and frequently such measures appear to have done more harm than good.

Replacement of blood and protein. Restoration of blood volume, measures to combat shock, and any procedure which tends to reduce renal vasoeonstriction and ischemia are of vital importanee during the early phase of acute renal failure. Time is of the essence and early recognition and immediate institution of therapy is of prime importance, since tubular injury from whieh the patient may not quickly recover may oeeur within the first few hours after the preeipitating episode and before acute renal failure is recognized clinically, if renal ischemia is severe. Administration of adequate volumes of plasma or of accurately typed, cross-matched whole blood, to restore a normal circulating volume during the early period of shock, is important. The use of concentrated human serum albumin may be indicated in order to maintain blood volume and to prevent, to some extent, exeessive dissipation of fluid into the extraeellular tissues. Yet, these measures must be used with extreme caution lest hypervolemia with consequent myocardial decompensation result.

Vasodilating agents. Heat, in the form of hot paeks or diathermy applied to the renal regions,

may help increase the renal blood supply and produce renal vasodilatation. The effectiveness of this measure is not established. Roentgen rays, likewise, have been applied over the kidneys in an attempt to induce renal vasodilatation. Aminophylline in doses of 3.75 to 7.5 gr. (0.25 to 0.48 gm.) has been given intravenously, either separately or added to each liter of intravenously injected fluid, for the purpose of producing renal vasodilatation. Intravenous administration of histamine diphosphate has been suggested as a means of producing renal vasodilatation. Ethyl alcohol in a concentration of 5 per cent in a 5 per cent solution of dextrose in distilled water has been given intravenously, and, in an occasional mild case, formation of urine has appeared to increase somewhat. Sympathicolytic agents, such as tetraethylammonium chloride or hexamethonium bromide, have been administered for the purpose of blocking renal sympathetic stimulation and renal vasoconstriction. Such measures have been without effect, however, and it is probable that resultant hypotension from use of these drugs may be more deleterious than helpful. Procaine hydrochloride in 0.1 per cent solution in an isotonic solution of sodium chloride given intravenously has been used, and some authors agree that results are sufficiently good to justify its use in patients suffering from acute renal failure.

Diuretic agents. Use of diuretic agents in the early period should be condemned. Mercurial diuretics never should be used in the presence of anuria or oliguria lest mercurial intoxication ensue with further damage to the already damaged renal tubular cells. Administration of acid-salt diuretics — ammonium chloride, potassium chloride, ammonium nitrate, and potassium nitrate — likewise is ill-advised. Use of potassium salts, as diuretics, introduces the serious hazard of potassium intoxication. Use of chloride salts to promote diuresis is apt to produce hyperchloremia and acidosis. In my opinion, intravenous administration of magnesium sulfate as a diuretic has no place in the treatment of acute renal failure. The sulfate radical is known to be toxic, is excreted with difficulty, and may be retained in high concentration in the presence of renal insufficiency.[8] In addition, although little is known of the metabolism of magnesium in man, evidence indicates that retention of the magnesium ion, in the presence of renal insufficiency, may play a role in development of the mental symptoms and stupor which accompany the uremic state. Sodium sulfate given intravenously in a 5 per cent solution has been advocated as a suitable diuretic for use against oliguria or anuria.[9] However, it seems hazardous to add to the body in sizable quantity a substance known to be toxic to the organism and one which the body is incapable of excreting satisfactorily. Use of parathyroid extract as a means of inducing diuresis in patients suffering from acute renal failure has been suggested,[10] but there is little or no clinical evidence to indicate that this measure is effective.

If passive backward diffusion of metabolites, electrolytes, and water from the lumen of the tubules across injured tubular cells into the blood plasma is a major factor in production of acute renal failure and oliguria, as has been concluded by some, then introduction of an inert substance, which is neither secreted nor excreted by tubular cells into the tubular lumen, should increase osmotic pressure of the tubular fluid sufficiently to offset the osmotic "pull" of plasma protein, thereby preventing back diffusion. On the basis of this assumption, mannitol, a substance which ordinarily is secreted by glomerular filtration and passes unaltered through the tubular system, has been advocated as a tubular diuretic. Intravenous administration of 100 cc. of mannitol in a 25 per cent solution on two or three successive days has been used in some cases and has seemed helpful in promoting formation of urine.

Surgical measures. Paravertebral block of the renal sympathetic ganglia with procaine hydrochloride should be helpful if renal suppression is due to ischemia secondary to renal vasoconstriction. In my experience, paravertebral block has not been eminently successful in increasing the formation of urine in the presence of acute renal insufficiency, although successful use of this measure has been reported in the literature from time to time.[11–13] Favorable responses to spinal or caudal anesthesia in cases of anuria have been reported also.[14–16]

Decapsulation of the kidney for renal insufficiency has been advocated on the basis that it reduces edema of the renal parenchyma and interrupts impulses along vasoconstrictor nerve pathways.[17] Advocates of this procedure have stated that it must be done within the first day or two after onset of suppression of urine. Antagonists of the procedure have expressed the belief that, if it is performed at an early stage, a rather hazardous surgical procedure may be inflicted on a patient who would probably recover with the use of conservative measures only.[18] They have said further that if decapsulation is deferred until conservative measures fail to produce resumption of urinary excretion, then the risk becomes greater and is almost prohibi-

tive. At present the bulk of evidence is against decapsulation in the treatment of renal insufficiency.

MAINTENANCE DURING THE PERIOD OF OLIGURIA OR ANURIA

Many cases of acute renal insufficiency with oliguria can be prevented. Study of a series of cases discloses that the syndrome often occurs in the patient whose state of hydration or circulating blood volume has not been satisfactorily maintained. Severe dehydration, losses of water and electrolytes, may induce oliguria and uremia which can be greatly improved by proper replacement therapy. After renal parenchymal damage has occurred, however, no amount of fluid will effect restoration of urinary formation until the tubular lesion has healed sufficiently to allow resumption of renal function.

Dietary measures. Dietary measures designed to improve nutrition are highly valuable. Anorexia, which nearly always presents a serious problem, and nausea and vomiting must be dealt with energetically. Unfortunately, certain restrictions necessitated by renal insufficiency — notably, restricted intake of protein and salt — may result in a highly unpalatable diet which further reduces the patient's desire to eat. Intake of protein should be reduced to a minimum in order to lessen the excretory load that protein metabolism imposes on the kidney, and also to prevent increase of azotemia and further renal damage; yet the diet must be sufficiently high in carbohydrate and fat so that the protein-sparing properties of these foodstuffs will prevent breakdown of endogenous stores of protein and the patient will be kept in positive nitrogen balance. The rice-fruit diet of Kempner,[19] the high-carbohydrate, high-fat, low-protein diet suggested by Borst,[20] and the protein-free, high-carbohydrate, high-fat formula of Bull[21] should be ideally fitted to serve this purpose. Borst has expressed the opinion that, if the patient can be provided a low-protein or protein-free diet sufficiently high in carbohydrate and fat to prevent breakdown of endogenous protein, the rate of accumulation of nitrogenous and other waste products in the blood will be retarded, and the patient can be maintained in better condition during anuria. This dietary program has been employed at the Mayo Clinic in a number of cases of acute and renal failure with satisfactory results.[22]

Unfortunately, however, to carry out a successful dietary program is difficult for many patients because anorexia, nausea, and vomiting prevent adequate oral intake and necessitate parenteral administration of supplemental nutritional substances.

Parenteral therapy. For the reason just stated, and because of the extreme importance of electrolyte balance and water balance to a patient with acute renal insufficiency, parenteral administration of fluid is of paramount importance. Some have advocated use of 10 or 15 per cent solution of dextrose in distilled water to provide a high caloric intake. Thorn[23] stated that during the early stage of anorexia and vomiting, intravenous infusion of a 15 per cent solution of glucose will reduce breakdown of endogenous protein. Yet a hypertonic solution must be used with great caution in order that fluid will not be pulled from the extracellular spaces into the circulating blood, with consequent production of hydremia, which might result in pulmonary edema and congestive heart failure.

The volume of fluid to be given parenterally is of great importance and, on this factor alone, may depend the success or failure of treatment. Attempts to force the renal block or to flood the body with fluid in the hope of increasing production of urine may result in overwhelming peripheral edema, pulmonary edema, and death.

Care must be used in determining the quantity of fluid to be given parenterally, in view of the fact that the patient's main avenue of fluid excretion has been blocked. Maddock and Coller[24] stated that a normal individual excretes each day from 600 to 1,500 cc. of water in the urine, 150 to 200 cc. in the stool, and 1,000 to 1,500 cc. in vaporization from the skin and lungs — the so-called insensible loss of fluid. Thus, the normal individual requires daily approximately 1,500 to 3,000 cc. of fluid in order to maintain adequate water balance. For the patient who has anuria or oliguria, however, a nearly normal state of hydration can be maintained by daily administration of fluid equal in volume to the estimated insensible loss of 1,000 cc. plus a volume equal to the urinary output. If the patient has a high temperature or is losing an excessive amount of fluid through perspiration, through a nasal tube, or through some other abnormal avenue of escape, then the volume of fluid lost must be added to the amount required to keep the patient in adequate fluid balance. In general, if the patient has a normal temperature and is not losing fluid through other routes, approximately 1,500 cc. of fluid daily, given parenterally, is adequate to maintain fluid balance.

As long as the concentration of chloride in the blood plasma is normal, sodium chloride need not be given parenterally. Rather, a 5 per cent solution of dextrose in distilled water is the fluid

of choice. An excessive intake of salt invites retention of water and edema. If, however, loss of gastrointestinal secretion is abnormal, such as occurs in vomiting, gastric aspiration, or intractable diarrhea, then serum sodium or plasma chlorides may be depleted and, if hypochloremia or hyponatremia is present, administration of sodium chloride in an 0.8 per cent solution alone or 5 per cent dextrose made up in 0.8 per cent solution of sodium chloride may be indicated to replace the chloride or sodium lost. The indication for sodium chloride in the parenteral fluids can be determined only by careful observation of the concentration of chloride in the plasma from day to day. In an occasional case, the loss of chloride is greater than can be replaced by the use of physiologic saline solution, or it is desirable to replace chloride without the addition of an excessive amount of sodium. This is particularly true in the presence of peripheral edema. Under these circumstances, rather sizable quantities of chloride can be administered cautiously in an 0.8 per cent solution of ammonium chloride; volumes of from 500 to 1,000 cc. can be given intravenously daily.[25,26]

Some argue against the intravenous administration of ammonium chloride in the presence of acute renal failure, on the ground that additional nitrogen may be deleterious. Ammonium chloride has been given intravenously in a number of cases and untoward results have not been encountered, nor, in my experience, has any increase in renal insufficiency been observed after its use.* When acidosis is present, solutions of sodium bicarbonate or sodium lactate introduced intravenously may be necessary. Sodium bicarbonate may be given in a 5 per cent solution intravenously in volumes of 250 to 500 cc. Sodium lactate in sixth-molar concentration may be used in volumes of 500 to 1,000 cc. I have found the former solution preferable because it produces more bicarbonate at the time of injection than does the solution of sodium lactate. The indication for use of either solution must rest on daily determination of the carbon dioxide combining power of the plasma.

Collateral therapy. Since the nutritional state of the patients usually is far below normal, all fluids for parenteral administration should be adequately fortified with vitamins B and C. If the serum calcium of the patient is found to be seriously depleted, as occasionally is so in the presence of acute uremia, intravenous administration of 20 to 40 cc. of calcium gluconate may be indicated daily. Digitalis, if indicated, may have to be given by the parenteral route because of the intense nausea and vomiting. Digitoxin in a dose of 0.1 to 0.2 mg. or 2 to 4 mg. of lanatoside C (Cedilanid), given intravenously each day, should be sufficient for maintenance after digitalization has been accomplished.

Small transfusions of whole blood or of washed fresh packed erythrocytes are the most satisfactory means of combating the anemia which accompanies acute renal failure.

Hyperkalemia, as determined by the appearance of high-peaked T waves, prolonged Q-R intervals, loss of P waves in the electrocardiogram, and by elevated values for potassium in the serum may complicate acute renal failure and may be an important cause of death. Acute retention of potassium may be treated successfully by intravenous infusions of 5 per cent dextrose in isotonic solution of sodium chloride, and, in some instances, with the addition of 10 cc. of a 10 per cent solution of calcium gluconate to the infusion. In addition, it is advisable to rigidly restrict the intake of potassium and to administer, either 15 gm. three times daily orally or 50 gm. in 200 to 300 cc. of water by enema twice a day, a cation exchange resin in the ammonia or sodium cycle.

Under this regimen, if the patient's fluid and electrolyte balance can be adequately maintained and if development of uremic symptoms can be forestalled for a sufficient length of time, reversal of the renal condition may occur and, with anatomic and physiologic regeneration of adequately functioning renal tissue, resumption of renal function may take place. The recuperative power of the kidney cannot be underestimated. A large percentage of patients with acute renal failure on the basis of a reversible renal lesion recover on a conservative program such as has been described.

If, however, at the end of five to seven days, there has been no indication of resumed urinary excretion; if the values for urea, sulfate, phosphate, and other metabolic waste products in the blood continue to rise; and if the symptoms and signs of clinical uremia develop in spite of conservative measures, extrarenal means may be necessary to relieve the uremia. Various methods have been described for clearing metabolic waste products from the body as a means of sus-

*1,000 cc. of 0.8 per cent solution of ammonium chloride contains 8 gm. of ammonium chloride or 2.1 gm. of nitrogen $\left(\frac{14 \times 8}{53.5}\right)$; 2.1 gm. of nitrogen would be converted to 4.5 gm. of urea (2.1 x 2.14). If a patient weighed 60 kg., the addition of 4.5 gm. of urea would increase the concentration of urea in blood and tissues by approximately 7.5 mg. per 100 cc. $\frac{(4{,}500 \times 100)}{60{,}000}$.

taining patients through the critical or anuric period until the kidneys are capable again of forming urine. Such methods include continuous lavage of the stomach and upper part of the small bowel, peritoneal lavage, and extracorporeal dialysis, "artificial kidney." These methods are not new, extracorporeal dialysis having first been suggested in 1914[27] and peritoneal lavage in 1923,[28] but knowledge of them and their use has been extended by the work of Kolff and Berk,[29] Murray and associates,[30] Frank, Seligman and Fine,[31,32] and others.[33] The recent literature contains many clinical reports of patients with acute renal failure treated by one of the means mentioned. Because of the rather elaborate setups required, the relatively high percentage of failures, and the numerous technical difficulties involved in carrying out methods of extrarenal excretion, a conservative program of treatment tried for as long as possible cannot be emphasized too strongly. However, if conservative measures fail and death appears likely, then one of the methods of extrarenal excretion should be seriously considered as a lifesaving measure.

MANAGEMENT OF THE POSTANURIC PERIOD

When formation of urine is resumed and the onset of diuresis occurs, a second distinct hazard arises. With large volumes of urine passing through the kidneys, excessive quantities of sodium chloride are lost, resulting in depletion of the serum sodium or plasma chloride to critical levels.

The clinical state associated with hypochloremia, hyponatremia, and critical dehydration has been recognized for some time, but only in recent years has sufficient emphasis been placed on the importance of sodium deprivation.[34] Consequently, the physician must not relax his vigilance with the onset of diuresis, but must make frequent determinations of plasma chloride, the carbon dioxide combining power, and, when feasible, serum sodium throughout the period of diuresis. If concentration of these electrolytes appears to be decreasing rapidly, it may be necessary to replace these ions by the liberal use of solutions of sodium chloride given parenterally to augment a diet unrestricted in salt. Only by bearing this complication in mind can disaster be prevented when the patient appears to have withstood the period of anuria and to be recovering. Many deaths have occurred in the period of diuresis, undoubtedly because of inadequate treatment, when the underlying renal disease already had improved satisfactorily. Likewise, many deaths undoubtedly have occurred in the anuric period because of excessive administration of fluids or ill-advised electrolyte therapy, due to the misconception that oliguria and anuria can be combated by massive hydration alone.

SUMMARY

In summary, conservative management of acute renal failure on the basis of a reversible renal lesion is best considered in 3 categories: (1) prompt emergency treatment during the phase of renal damage, (2) maintenance during the phase of oliguria or anuria, and (3) reparative treatment during the postanuric period or phase of diuresis.

The first hazard lies in attempting to increase output of urine during the oliguric or anuric period by flooding the body with excessive amounts of salt, or with large volumes of fluids introduced parenterally. A second great danger is critical depletion of sodium and chloride from the extracellular fluid spaces of the body during the phase of postanuric diuresis.

Acute suppression of urine is always a catastrophe and the prognosis always should be guarded. Treatment is tedious and the mortality rate may be high. However, the widening horizons of knowledge in regard to pathogenesis of this condition and judicious conservative care will result in a striking increase in the recovery rate from acute renal failure.

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Lancet Editorial

A Record of Medical Progress

When The Journal-Lancet was 80 years old attention was called editorially to the marked progress that had been made in all phases of medicine since the first issue appeared in June 1870. Progress has continued and in many ways accelerated to this 85th birthday of the Journal.

When the first issue appeared in 1870, there was no medical school in Minnesota, no State Board of Health, and no school of nursing. The only organization extant was the State Medical Association organized in 1853, which held only a few meetings until it was revived in 1869. It was this organization for which Journal-Lancet began publication in June 1870. Over the next eighty-five years Journal-Lancet played a dominant role in medical and closely allied organizations by keeping physicians informed, thus stimulating interest in and support of all that was good. First accounts of the State Board of Health proposed by the State Medical Association together with its actual organization in 1872, and much of its subsequent activity were recorded in this Journal. This was also true of numerous other medical and health organizations which subsequently evolved, including schools of nursing, the first of which opened at Northwestern Hospital in Minneapolis in 1881, and medical and social work which began in 1915. A veterinary division was established in the University School of Agriculture in 1893. The State Livestock Sanitary Board was organized in 1903.

Small schools of medicine began to appear, the first in 1871. The creation of a department of medicine in 1883 and appointment of a teaching faculty of 29 members in 1888 resulted in gradual disappearance of the various small schools. Since 1908 only the University of Minnesota's school of medicine has been in operation.

Not until 1883 did the legislature pass an act to regulate the practice of medicine in Minnesota requiring all physicians to be licensed. This was a severe blow to quackery. Four years later a new medical practice act created an independent state board of medical examiners.

There was no organized effort to fight the first cause of death, tuberculosis, until 1890 when a tuberculosis association appeared at Willmar, one in Minneapolis in 1903, and the state organization now known as the Tuberculosis and Health Association in St. Paul in 1906.

Since 1870 accomplishments in all phases of medicine and surgery have far exceeded the fondest dreams and highest hopes of those who worked at that time.

Artificial immunization against diseases of which an attack results in dependable immunity such as smallpox, diphtheria, and typhoid fever together with other measures to prevent dissemination in communities have reduced these diseases to minor positions, but vigilance must be continuously exercised. Antimicrobial drugs beginning with sulfonamides and other chemicals and antibiotics have proved specific for many of the infections.

Tuberculosis, long the number one killer, has been reduced to the 14th cause of death in Minnesota. This accomplishment was achieved by alert medical and nursing professions and their allies along with tuberculosis and health organizations which provided so much information for the citizenry. Sanatoriums were built. Veterinarians fought this disease in cattle and other domestic animals. In 1911, 2,522 Minnesota citizens died from tuberculosis when the mortality rate was 119.7 per 100,000 persons living. In 1953, with a larger population, only 212 died, a rate of 6.9 per 100,000. Preponderance of illness and death from tuberculosis now occurs among persons in the later decades of life. These are the individuals who as infants and children had little protection against tubercle bacilli. The veterinary profession has all but eradicated tuberculosis from the 3,000,000 cattle of the state, so near in fact that now only 1 animal in each 5,000 tested harbors tubercle bacilli. Similar accomplishments have been achieved in other states in this general area.

Phenomenal advances have occurred in surgery. In 1922, Dr. A. A. Law said he could foresee the day when the chest, including the heart, would yield up its secrets to surgeons just as other parts of the body had already done. Now removal of lungs, lobes, segments, and smaller units for such conditions as bronchiectasis, abscess, malignancy, and tuberculosis have become commonplace. Cardiovascular diseases and conditions including patent ductus arteriosus, septal defects, stenosis, and even aortic conditions such as coarctation are now treated successfully by surgery.

Although advances have been made, there are diseases including leukemias, poliomyelitis, and malignancies which are still baffling. However, a large volume of research is being conducted by those with

the keenest and best informed minds, thus offering much promise even for these conditions.

It is particularly fitting that considerable space in this anniversary issue is devoted to the University Medical School which has developed from a meager beginning in 1883 to a position of second to none from the standpoint of teaching, research, and physical equipment in 1955. The faculty, which had 29 members in 1888, has more than 600 at the present time.

The illustrations in this issue of the Mayo Memorial Building, occupied and dedicated in the Fall of 1954, show the tremendous physical development of the school from a leased building some distance from the campus in 1888 and 1 small building on the campus known as Medical Hall in 1893.

As one scans the pages of JOURNAL-LANCET over the years from June 1870, through the present issue, one sees chronologically recorded the advances in all phases of medicine informing physicians of one generation after another of current progress. The same policy is scheduled to continue through succeeding years and decades.

J. ARTHUR MYERS, M.D.

The Surgery of Pulmonary Tuberculosis, by JAMES H. FORSEE, 1954. Philadelphia: Lea & Febiger. 208 pages, 59 illustrations, 11 graphs, 46 tables. $6.50.

The past ten years have brought such drastic changes in the treatment of pulmonary tuberculosis that all texts previously published on the subject have been rendered obsolete. The present volume is the first devoted exclusively to this subject which adequately portrays modern therapeutic programs in contrast to methods previously in use.

The book is divided into three parts: Part I, Principles in the Application of Surgery in Pulmonary Tuberculosis; part II, Operative Surgical Procedures, Past and Present; part III: Experience with Surgical Therapy in Pulmonary Tuberculosis (made from a study of approximately 1,000 patients treated by the various methods at Fitzsimons Army Hospital, Denver, 1947 to 1954).

The contrast between the methods used and the results produced in the past years and those now in vogue in the "chemotherapeutic and antibiotic era" is well brought out. Case histories, photographs of x-ray films, and specimens are used freely to illustrate the text. Discussions of indications for treatment, timing of the procedures, special technics, complications encountered, and results obtained add much to the value of the book. The necessity for cooperation between the various members of the therapeutic team is stressed repeatedly. The medical, roentgenologic, pathologic, and bacteriologic as well as the surgical aspects of the disease are given due consideration.

The style is slightly ponderous and the text somewhat monotonous because of the frequent quotation of statistics, but these are essential in presenting an analytic report of the contrasting programs of treatment.

The binding and paper stock are of good quality. The reproductions of x-ray films and photographs of specimens are good. The charts and graphs are clear and sharp cut.

The volume is a timely addition to our surgical texts. It may be scanned with interest and profit by many physicians and students who are not familiar with this changing field, and studied in detail by those already in the field. The book should be in all libraries so that students and residents may have ready access to it.

THOMAS J. KINSELLA, M.D.

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Physiological Cardiology, by ARTHUR RUSKIN, 1953. Springfield, Illinois: Charles C Thomas. $8.00.

In this monograph the author has attempted the laudable goal of presenting the physiology and especially the biophysical part of the physiology of the heart in such terms as will be relevant to medical students and practitioners. For the most part the book accomplishes the objective, although this reviewer would have preferred a less encyclopedic treatment with more meticulous attention paid to those aspects treated at all. The large mass of material presented may sometimes serve to confuse rather than enlighten those readers who are not specialists in cardiovascular problems. For the beginner there is a very useful list of references to some of the more significant papers and to many monographs on the subject. From the point of view of the expert the references are too scanty. The difficulty of presenting the currentlly known facts about the clinical physiology of the circulation should temper any criticism of this book. It is, in this reviewer's opinion, the best treatment since Harrison's "Failure of the Circulation" appeared. It should provide a useful source for students of clinical cardiology.

MAURICE B. VISSCHER, M.D.

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Pediatric Problems in Clinical Practice, edited by H. MICHAL-SMITH, Ph.D., 1954. New York: Grune and Stratton. 310 pages. $5.50.

This is one of the best books we have seen in a long time because it deals with so many important questions in regard to children. For instance, chapter 4 on the Schizophrenic Child by Lauretta Bender is most interesting. Only gradually are physicians beginning to realize that a schizophrenic can be recognized by an expert even during the first months or years of his life. Mental retardation can be recognized early, and sometimes a tendency toward epilepsy.

One finds that children with epilepsy may have an erratic mood and behavior; they may have good and bad days without adequate explanation for the bad days; there may be hypermotility with an excessive energy and drive; and they may be irritable. When the child goes to school he may have special difficulty with mathematics; he may find reasoning difficult as compared with the ability to memorize.

As William G. Lennox said on page 246, "In our series of 4,000

(Continued on page 34A)

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cases of all ages, 77 per cent had a first seizure in the first 2 decades of life. Of persons below the age of 20, the number with a history of seizures approaches one-half million." Among draftees, 1 in 200 was rejected because of continued epileptic attacks.

WALTER C. ALVAREZ, M.D.

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The Hypertensive Disorders of Pregnancy, by ERNEST W. PAGE, M.D. 1954, Springfield, Illinois: Charles C Thomas. $3.75.

This review of the hypertensive disorders of pregnancy is of value to the practicing obstetrician and internist because clinical aspects of the problem are evaluated. Furthermore, there are chapters on the physiologic and biochemical changes in normal pregnancy and in toxemia and also on the etiology of toxemia. The cause of toxemia of pregnancy remains unknown and therefore there are numerous speculations. Chemical mediators receive attention; the hypothesis that a "corticoid" of placental origin plus sodium chloride plays a role in the pathogenesis of toxemia is mentioned as attractive and deserving of continuing investigations. Whatever the chemical mediators may be, the greatest effect in the body is considered to be upon the blood vessels themselves. For instance, the sequence of vascular constriction, tissue hypoxia, and edema, if occurring in the brain, might lead to convulsions. An adequate bibliography is given.

C. A. MCKINLAY, M.D.

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Roofs for the Family, by EVA BURMEISTER, 1954. New York City: Columbia University Press. 203 pages. $3.25.

Miss Burmeister uses a narrative style to recount her experiences as director of a treatment home for children in Milwaukee. Although most of the book deals with the building of the physical plant for a children's home, wise and understanding sections are included about the children and how they live together. The author's knowledge of children and her gentleness in dealing with them are readily apparent.

The book was not written to prove a point nor to educate; it is a warm and simply written account of long experience and sound observation. *Roofs for the Family* will be of interest to all who have to do with the care and treatment of children, particularly those in group living situations.

WILLIAM FLEESON, M.D.

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Laboratory Aids in Endocrine Diagnosis, by ROBERTO F. ESCAMILLA, M.D., 1954. Springfield, Illinois: Charles C Thomas. 131 pages. $4.75.

The title of this monograph is informative as to its contents. It contains a useful and an enormous amount of information in relatively few pages.

The relationship of certain laboratory tests to specific endocrine disorders is emphasized throughout. Each chapter has key references to the method used, and it is complete. It is a valuable text for the physician in the study and diagnosis of endocrine disorders.

DONALD S. AMATUZIO, M.D.

American College Health Association News . . .

THE ANNUAL MEETING of the New England Section was held November 20 at the Austin Riggs Foundation under the chairmanship of Dr. Achsa Bean with the cooperation of Dr. Thomas Urmy of Williams College. Mr. Eric Erickson of the Foundation staff gave a splendid discussion entitled "Achieving Identity, A Normative Crisis of the College Age." Case histories of 2 young people of college age presenting different aspects of an identity problem were given by Dr. Graham H. Blaine and Dr. Cyrus R. Friedman, former and present psychiatrists, Williams College.

Dr. Clair B. Crampton of Wesleyan University, Middletown, Connecticut, volunteered to act as host for the 1955 meeting. Dr. Bryant Wedge of Yale University, department of university health, was asked to accept the chairmanship with responsibility for arranging the program.

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The Pacific Coast Section meeting was held December 3 and 4, 1954 at Sacramento State College, Sacramento, California. An excellent program was presented as follows: "The County Physician and the Student Health Service" by Ira O. Church, M.D., Sacramento County health department; "Some Aspects of the Physical Environment of the Student" from the standpoint of sanitation by Frank Gohr, division of sanitation and Margaret O. Dewell, of the student housing program, living accommodations inspector, both of the University of California at Berkeley; "Some Newer Findings in the Diseases of Animals Transmitted to Man" by John B. Enright, Ph.D., associate professor of public health, School of Veterinary Medicine, University of California at Davis; "Interdepartmental Relationships," a panel discussion by Chaffee E. Hall, associate dean of students; Barbara Kirk, manager counseling center; Joseph Wheelright, M.D., consultant psychiatrist, all of the University of California, Berkeley; Glen R. Leymaster, M.D., director, student health service, University of Utah; and Evelyn Clark, R.N., B.S., student health service, Whittier College. December 4 a symposium on "Prevention of Injuries to Students" was presented with the following participants: moderator, George H. Houck, M.D., director of health service, Stanford University; physician, Rodney R. Beard, M.D., clinical professor of occupational health, University of California and professor of preventive medicine, Stanford University; state department of public health (home accidents), Gilbert L. Rhodes, chief, home safety project, San Francisco; safety engineer, A. C. Blackman, chief, division of industrial safety, state of California; health educator, Alma Nemir, M.D., department of preventive medicine, University of Utah; psychologist, Harold R. Renaud, Ph.D., chief clinical psychologist, student health service, University of California at Berkeley.

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Bills for the 1955 annual dues have been mailed to all members and also a tentative program for the annual meeting and a brochure and reservation blank from the Broadmoor Hotel at Colorado Springs. We hope all members will be represented at the Colorado Springs meeting and suggest that requests for reservations be sent to the Broadmoor Hotel as soon as possible.

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

Use of Cobalt and Iron in the Treatment and Prevention of Anemia of Prematurity

BETTY L. COLES, M.D., AND URSULA JAMES, M.D.
London, England

THE PATHOGENESIS of the anemia of prematurity is still somewhat obscure, but the blood picture closely resembles that of anemia associated with infection. In each case the anemia is of normocytic and normochromic type with a low reticulocyte count, and this similarity between the anemia of prematurity and that of sepsis led us to investigate the effect of cobalt in premature infants.[1] It has been suggested by Wintrobe and associates[2] that cobalt may be needed in the synthesis of hemoglobin in the anemia of sepsis. Vaughan[3] referred to this in a paper on the anemia of sepsis and trauma, and suggested cobalt as a possible treatment in anemia resulting from infection.

PRESENT INVESTIGATION

Technic employed. Red cell counts were made with an improved Neubauer counting chamber using normal saline and methyl violet as a diluting agent, and the hemoglobin was estimated by the Sahli method in which 14 gm. of hemoglobin equals 100 per cent. In the neonatal period, the blood-acid mixture was allowed to stand an hour before readings were made, as Whitby and Britton[4] point out that fetal hemoglobin takes longer to convert to acid hematin than the adult type, and falsely low results may be obtained if this fact is not taken into account. The same counting chamber, standard, and glassware were used throughout the investigation to obtain comparable results, and all blood was taken and examined by Dr. Coles. Blood was obtained in all cases by heel puncture.

The cobalt sulfate used was the B.D.H. analar salt which is freely soluble in water and practically tasteless. The iron mixture was prepared according to Mackay's formula, and was given in 3 divided doses.

Investigations were made of 126 infants born at 4 maternity units and 83 were followed for six months or longer. Four other infants were excluded from the series, 1 on account of hemorrhage from the cord and 3 because of death in the neonatal period.

The cases were divided at random into 4 groups as follows: group 1, controls; group 2, received 10 mg. of cobalt sulfate daily by mouth from one to twelve days of life inclusive; group 3, received 20 mg. of cobalt sulfate daily by mouth from four to eight weeks; group 4, received 20 mg. of cobalt sulfate by mouth, together with 4.5 gr. of ferrous sulfate daily from four to eight weeks.

Blood counts were made in all infants at birth, one week, two weeks, one month, and at monthly intervals to six months. In some cases, counts were continued up to one year. We adopted an

BETTY L. COLES, *a 1946 graduate of Royal Free Hospital School of Medicine, London, is research assistant in pediatrics at Royal Free Hospital.* URSULA JAMES, *a 1937 graduate of the same school, is children's physician to St. Mary's Hospital, Victoria Hospital for Children, Elizabeth Garrett Anderson Hospital, General Lying-In Hospital, and Annie McCall Maternity Hospital, all in London.*

arbitrary level at which further treatment was instituted if anemia developed during the course of the investigation. Cobalt sulfate, 20 mg. daily, was given to any infant whose red cell count fell below 2.5 M. per cu. mm. if the hemoglobin was below 70 per cent at that time, and ferrous sulfate, 4.5 gr., was given to infants with hemoglobin below 70 per cent at any age. Infants aged 6 months with hemoglobin below 75 per cent for two consecutive months were also given iron in order to prevent a severe iron deficiency anemia. In patients requiring additional iron therapy at 6 months, the blood was examined monthly until therapy ceased and satisfactory blood levels were obtained. The data of all cases needing additional cobalt or iron therapy have been removed from the statistical analysis, and these results are expressed separately.

All infants were either breast fed or received dried or evaporated milk made up of 20 calories to the ounce. Vitamins A, D, and C were started as soon as feeding was satisfactorily established, usually at about the tenth day, and solids were introduced in all cases between three and a half and five months. Where possible, the infants attended special follow-up clinics attached to the maternity unit, but where distance or domestic duties made this impossible they were visited at home. Records of weight and clinical progress were made at each visit.

RESULTS

During the first twelve days of life, 20 patients receiving cobalt and 18 controls had blood counts on the fourth, eighth, and twelfth days. The average fall of hemoglobin and red cells below birth level on each day is shown in table 1. The infants having cobalt showed a less pronounced fall in both hemoglobin and red cells, but the differences are not significant. Statistical analysis shows that these infants, group 2, had slightly higher average hemoglobin and red cell counts than the controls, group 1, at each month up to six months, but only the hemoglobin level at two months, and the red cell counts at one, two, four, and five months showed significant differences at the 5 per cent level (table 2).

TABLE 1
AVERAGE FALL OF HEMOGLOBIN AND RED BLOOD CELLS BELOW BIRTH LEVELS DURING FIRST 12 DAYS

	4th Day		8th Day		12th Day		
Group	Hb. (%)	RBC (M.)	Hb. (%)	RBC (M.)	Hb. (%)	RBC (M.)	No. of Cases
1	6.55	0.40	16.77	0.82	23.71	1.26	18
2	5.85	0.42	10.95	0.80	22.00	0.88	20

Group 1.—Controls.
Group 2.—Cobalt sulfate, 10 mg., 1 to 12 days.

TABLE 2
STATISTICAL ANALYSIS OF AVERAGE HEMOGLOBIN AND RED CELL COUNTS TO SIX MONTHS OF AGE

Number of Cases	Group 1		Group 2	
1 mo.	35		20	
6 mo.	21		12	
	Hemoglobin	Red blood cells	Hemoglobin	Red blood cells
Birth	21.75	5.76	21.50	5.98
1 mo.	14.40	3.96	15.10	°4.42
2 mo.	10.78	3.34	°11.81	°3.79
3 mo.	10.78	3.57	10.97	3.66
4 mo.	10.93	3.70	11.61	°4.17
5 mo.	10.93	3.91	11.66	°4.30
6 mo.	11.35	4.19	11.83	4.27

°The difference between this pair of means is significant at the 5% level.

Control values for both hemoglobin and red cells are well below those seen in groups 3 and 4 (chart 1).

In view of the small effect of early administration of cobalt, the data for this group of infants has been amalgamated with that for the control group to give a more dependable standard against which to assess any effect of giving cobalt from one to two months. Infants who received cobalt from one to two months, groups 3 and 4 combined, had a significantly higher average hemoglobin content and red cell count at each examination from two months onward than groups 1 and 2 combined. Infants in group 4 had statistically significant higher hemoglobin contents from four to six months than group 3 who also received cobalt but no iron. At this stage, iron deficiency becomes important in the development of anemia in premature infants, and these results were to be expected. The red cells appear unaffected by iron (chart 2).

There were 3 patients in the group needing additional cobalt therapy and all were in the control group. A fourth control case, P. S., with

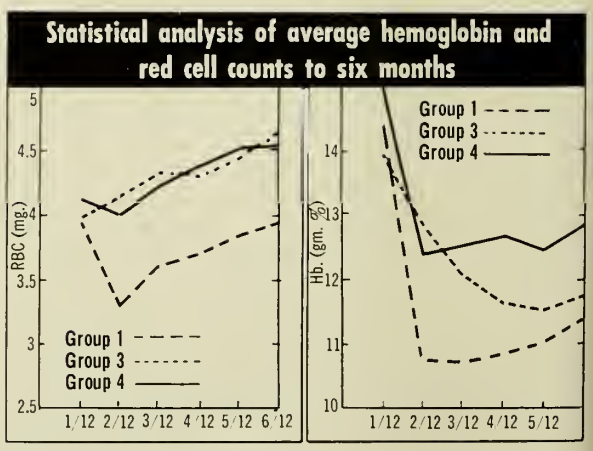

Chart 1.

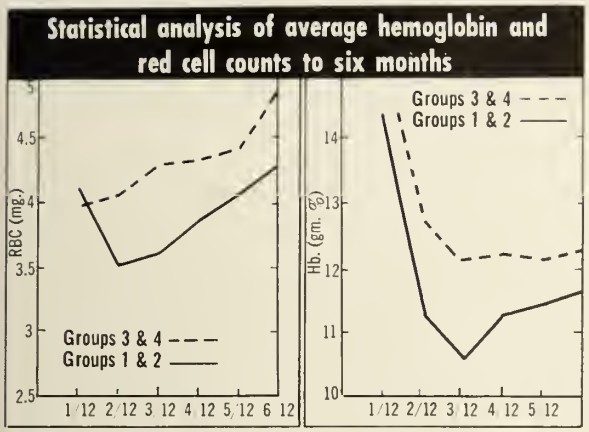

Chart 2.

a count of 66 per cent hemoglobin and 3.08 M. per cu. mm. red cells, had severe symptoms of anemia with anorexia, lassitude, and extreme pallor, and, therefore, he was given cobalt although the count had not reached the critical level determined upon for treatment. The response to treatment was satisfactory (table 3), but the 2 children of five months were obviously suffering from coincidental iron deficiency necessitating administration of iron before the hemoglobin levels rose, although the red cells responded to cobalt alone. It is important to emphasize that no case of early anemia in our premature infants required blood transfusion.

In 14 patients, the hemoglobin fell to levels which required iron therapy. Of these cases, 8 were controls, group 1; 3 were in group 2; and the other 3 were in group 3. The details of these cases are shown in table 4.

We feel it is significant that no case receiving iron and cobalt from four to eight weeks required any additional therapy, that all the infants needing additional cobalt were in the control group, and that 57 per cent of cases given additional iron therapy were also from the control group. It has been suggested by Kato and Iob,[5] Wintrobe and associates,[2] and Gubler and associates[6] that cobalt favorably influences the utilization of iron for hemoglobin synthesis, and these results appear to confirm this hypothesis.

The symptoms of the infants who developed anemia were confined to pallor except in the baby, P. S., already mentioned. However, after treatment with iron or cobalt, the mothers of these anemic children frequently stated spontaneously that their children were much improved, with better appetite and more energy. It seems, therefore, that there is a subclinical debility associated with the anemia of prema-

TABLE 3

DATA FOR CASES OF THERAPEUTIC COBALT

Name and birth weight	*Prematurity in weeks*	*Age cobalt started*	*Duration of therapy*	*Hb. (%) Before*	*Hb. (%) After*	*RBC (M.) Before*	*RBC (M.) After*
R. W. 3.10. (twin)	5	2 mo.	1 mo.	65	86	2.15	4.32
J. B. 3.15. (twin)°	3	5 mo.	2 mo.	52	70	2.58	4.70
A. Q. 4 lb. (twin)	4	2 mo.	1 mo.	69	79	2.48	3.58
P. S. 4.9	2	5 mo.	1 mo.	66	60	3.08	4.16

All cases controls. Dosage 20 mg. daily.
°Plus iron for second month of treatment.

TABLE 4

DATA FOR CASES REQUIRING IRON

Name and birth weight	*Prematurity in weeks*	*Group*	*Age iron started*	*Duration of therapy*	*Hb. (%) Before*	*Hb. (%) After*	*RBC (M.) Before*	*RBC (M.) After*
J. B. 3.15° (twin)	3	1	6 mo.	4 mo.	55	89	4.24	4.98
P. S. 4.9°	2	1	6 mo.	did not attend	60	did not attend	4.16	did not attend
J. A. 4.0	7	1	6 mo.	3 mo.	74	100	4.84	4.46
S. T. 3.15 (twin)	7	1	6 mo.	2 mo.	74	88	3.84	4.06
A. K. 4.13	Term	1	6 mo.	3 mo.	71	90	4.18	4.80
G. A. 4.12 (twin)	2	1	6 mo.	3 mo.	57	90	3.48	4.50
K. B. 4.1	8	1	6 mo.	5 mo.	64	69	3.92	4.32
M. C. 5.4	5	1	9 mo.	did not attend	60	did not attend	3.94	did not attend
R. F. 5.3	Term	2	5 mo.	7 mo.	69	64	4.92	4.45
P. B. 3.13 (twin)	3	2	5 mo.	5 mo.	57	82	3.46	5.12
A. A. 4.10	2	2	6 mo.	did not attend	66	did not attend	4.24	did not attend
P. B. 4.12 (twin)	7	3	4 mo.	2 mo.	53	70	3.65	3.77
M. O.'D. 3.13 (twin)	7	3	9 mo.	2 mo.	72	95	4.22	5.08
N. S. 4.3	Term	3	5 mo.	5 mo.	63	80	4.00	4.70

°After one month of cobalt

TABLE 5

INCIDENCE OF BREASTFEEDING

Group	Number of infants	Breast fed (%) Fully	Partly	Never
1	21	53.8	38.6	7.6
2	15	36.8	36.8	26.4
3	28	31.2	46.9	21.9
4	21	25.9	48.2	25.9

TABLE 6

AVERAGE GAIN OVER BIRTH WEIGHT AT TWO, FOUR, AND SIX MONTHS

Group	Number of infants	Average birth weight	Average gain over birth weight (oz.) 2 mo.	4 mo.	6 mo.
1	21	4.11	57.0	118.4	169.2
2	15	4.7	61.9	117.5	173.9
3	28	4.7	57.7	114.7	160.8
4	21	4.10	47.0	104.1	156.3
1 and 2	36	4.9	59.1	118.0	171.1
3 and 4	49	4.8½	53.1	110.1	158.9

turity even where more definite symptoms are absent, and that this becomes more evident in retrospect.

It has been shown by Mackay[7] that artificially fed infants are more prone to anemia than those receiving breast milk, and that when anemia develops, it is more severe in the artificially fed. Consideration of our figures (table 5) makes it clear that the more satisfactory blood counts obtained in our treated cases were in no way due to breast feeding, as the incidence of breast feeding was considerably higher in the control group. This was entirely fortuitous since the cases from each group were selected at birth before feeding had begun.

There is conflicting evidence concerning the effect of cobalt on appetite and weight gain in both man and animals, and, therefore, the weights of all our infants were recorded at each attendance. The average weight gain in ounces over birth weight at two, four, and six months are shown for each group in table 6. The birth weights in the 4 groups were comparable, and the differences in weight gain are not significant.

Cobalt sulfate was readily taken in water or milk, and no signs of toxicity or impairment of appetite or vigor in any case under treatment was noted with the dosage employed.

DISCUSSION

There is a considerable literature on the experimental use of cobalt in producing polycythemia both in normal and anemic animals, but reports on the therapeutic use of cobalt in man are few. A discussion of this literature appears in an earlier paper by Coles and James in 1954.

Cobalt has been used in premature infants by Schmoger[8] and Quilligan[9] who both found that cobalt combined with iron resulted in higher hemoglobin and red blood cell levels than in untreated infants. The reticulocyte response in Quilligan's cases occurred ten days after the hemoglobin changes were first noticed, and he postulated that the greater hemoglobin and hematocrit values in the treated cases might be due to a delay in the red cell breakdown as well as to actual stimulation of the bone marrow. Schmoger treated 20 infants with cobalt amino-acid complex and iron, and these infants showed more satisfactory blood levels than the 20 infants treated with cobalt amino-acid complex alone. We are in full agreement with these findings, and we recommend the use of cobalt for the prevention of the early anemia of prematurity combined with iron to counteract the iron deficiency which almost inevitably develops later in these infants. The effect of the combined therapy of cobalt and iron for four to eight weeks is well shown in the hemoglobin and red blood cell levels in our group 4 patients compared with those of the other 3 groups. Our dosage of cobalt has been arbitrary and based on existing reports of the therapeutic use of cobalt in man, together with the doses used to produce polycythemia in animals. Possibly more prolonged treatment might be of greater benefit, and we feel that further work is necessary before the role of cobalt in prevention of the anemia of prematurity can be fully defined.

SUMMARY AND CONCLUSIONS

The study included 126 infants who were divided into 4 groups. Of these, 83 were followed for six months or longer. Group 1 acted as controls. Group 2 received 10 mg. of cobalt sulfate daily from one to twelve days. Group 3 received 20 mg. of cobalt sulfate daily from four to eight weeks. Group 4 received 20 mg. of cobalt sulfate and 4.5 gr. of ferrous sulfate daily from four to eight weeks.

Cobalt appears to be of value in the prevention of early anemia of premature infants, and, if iron is administered simultaneously, the risk of an iron deficiency anemia developing after the fourth month is considerably reduced. Cobalt has no toxic effects and no unfavorable influence on the weight gain in the dosage employed. The mode of action is uncertain but 2 possibilities seem likely: (1) a direct action on the erythropoietic tissue in the marrow; (2) a possible cata-

(Continued on page 42A)

Histoplasmosis

A Review with an Epidemiological and Clinical Study of an Outbreak Occurring in Minnesota

RICHARD T. SMITH, M.D.

Minneapolis, Minnesota

Since Darling's original description[1] of histoplasmosis one-half century ago, the concept of this disease has undergone a dramatic evolution. Originally considered to be an exotic tropical malady, histoplasmosis is now known to be a distinct mycosis of widespread geographic distribution, of diverse clinical manifestations, and of major medical importance. Many questions concerning the etiology of the fungus and the epidemiology of the human and animal disease remain unanswered. Epidemic outbreaks have offered the best opportunities for investigation of these aspects of the disease and much recent progress has been made.[2–5]

During the past year, an epidemic of histoplasmosis occurring in Wright County, Minnesota, has been discovered and its clinical and epidemiologic aspects have been studied. In addition, a survey of the prevalence of skin sensitivity to histoplasmin in the area of the epidemic has been conducted. The purpose of this report is to describe the clinical and epidemiologic aspects of the epidemic and the other investigations which resulted, and to attempt to evaluate the findings in terms of present concepts of the disease.

HISTORICAL REVIEW

The literature on histoplasmosis has been reviewed by several authors in recent years.[3,6–13] This review, therefore, is an attempt to elucidate critical developments responsible for present understanding of the disease and is not intended to be exhaustive.

The first example of the systemic mycosis now recognized as histoplasmosis was described in 1906 by Darling,[1] as "a protozoan general infection producing pseudotubercles in the lungs and focal necrosis in the liver, spleen, and lymph nodes." He first studied a 27-year-old Negro from Martinique who had died of a progressive disease characterized by fever, splenomegaly, anemia, neutropenia, and emaciation. He demonstrated, in the mononuclear cells of the liver, lymph nodes, and spleen, microorganisms morphologically similar to those seen in kala-azar.[14] This microorganism lacked the kinetoplast of the Leishman-Donovan body, and possessed a characteristic achromatic refractile rim. He considered the infecting agent to be a protozoon, named it *Histoplasma capsulatum*, and referred to the disease as histoplasmosis.[15]

In 1912, H. da Rocha Lima[16] reviewed Darling's cases, comparing *H. capsulatum* with a fungus, *Cryptococcus farciminosus*, which causes epizootic lymphangitis in horses. He concluded that *H. capsulatum* was probably a fungus. According to the De Monbreun,[17] Darling later concurred in da Rocha Lima's interpretation.

The reports by Watson and Reilly,[18] in 1926, of a fatal case of histoplasmosis originating in Minnesota provided impetus for the study of the disease in the United States.

The etiology of histoplasmosis was established securely by the work of De Monbreun in 1934,[17] in collaboration with Dodd and Tompkins.[19] They observed *H. capsulatum* in peripheral blood smears and bone marrow taken during life from a 6-month-old infant, and they cultured a fungus from these same tissues taken at necropsy. De Monbreun showed that the parasitic form of *H. capsulatum* which multiplies in the reticuloendothelial cells of the diseased patient is a fungus which remains yeast-like when cultured at 37° C. in enriched media, but reverts to mycelial-type growth and begins spore formation when grown under less favorable conditions. He described the identifying spore form —the tuberculate chlamydospore—suggested that this was the infecting form of the fungus, and inferred correctly the essential saprophytic nature of *H. capsulatum*. He further fulfilled Koch's postulates by producing infection serially in monkeys, puppies, and mice, and in 1939[20]

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

reported the natural occurrence of histoplasmosis in dogs.

Observations on infection by *H. capsulatum* in animals were reported by Tager and Liebow[21] who showed that rats, guinea pigs, hamsters, and chick embryos were susceptible to the fungus. Investigations of the prevalence and nature of infection by this fungus in domestic animals have been reported in recent years by Menges[22,23] and will not be reviewed here.

Conant,[24] using suitably enriched media, completed knowledge of the life cycle of the fungus by demonstrating the transformation from mycelial to yeast phase in vitro.

Van Pernis and associates[25] and others[26] developed a skin test antigen for diagnostic use in humans based on the demonstration of bacterial type hypersensitivity in experimentally infected animals, and in proved human infections.

In 1947, Iams and associates[11] reviewed 21 previously reported cases of the disseminated form of histoplasmosis occurring in children. From this material the frequency of occurrence of various clinical and pathologic features of the disseminated disease in children was determined. Of the 21 patients, 12 were under 8 months of age. Fever occurred in all of the children, weight loss and anemia, hepatosplenomegaly in 17 out of 21, lymphadenopathy in 9 out of 21, and leukopenia were commonly observed. At autopsy, infiltrations by the yeast form of the fungus were observed in the lungs, lymph nodes, liver, spleen, intestines, and bone marrow, in order of decreasing frequency.

From the time of Watson and Reilly's report until 1945, 77 cases[6] were described in the literature, most of which exemplified the progressive, almost uniformly fatal, systemic involvement of the reticuloendothelial system. The view was widely held that histoplasmosis was an uncommon disease occurring principally in young children, always having a poor prognosis.

The studies of Christie and Peterson,[27] of Palmer,[28] and of Furcolow and associates[29] showed that histoplasmosis is a widespread infection which is usually benign and often asymptomatic. Reasoning from his observations on coccidioidomycosis in southwestern United States, Smith[30] suggested in 1944 that the large numbers of tuberculin-negative draftees from the central Mississippi Basin, shown by roentgenograms to have pulmonary calcifications, might have had infection with *H. capsulatum* which was not apparent. Christie and Peterson[27] then fortified this concept with substantial data. They tested 2,032 persons residing around Nashville, Tennessee, who had nontuberculous pulmonary calcifications and found from 59.4 per cent to 83.9 per cent to be reactors to histoplasmin. Christie[31,32] later extended these observations and reviewed available evidence concerning the prevalence of skin sensitivity to histoplasmin throughout the world.

Palmer[28,33] reported studies in a large group of nursing students from various sections of the United States. He tested the correlation between pulmonary calcifications and skin-test reaction, and found that approximately 25 per cent of the entire group reacted to histoplasmin while 85 per cent of those with pulmonary calcifications were histoplasmin reactors. Furcolow and associates [29,34,35] and Beadenkopf and associates[36] added to the evidence that histoplasmin sensitivity was frequently associated with nontuberculous calcification, and provided further information on geographic distribution.

From these and subsequent studies, histoplasmin reactor rates for most sections of the United States have been determined. Various aspects of this problem have been reviewed.[4,12,31,33,37] The geographic distribution of high rates of sensitivity to histoplasmin has been found to include the western slope of the Appalachians and the central Mississippi Valley extending to Ohio in the east, Kansas in the west, south to Louisiana, and north to Minnesota, with highest rates in Kentucky, Tennessee, Missouri, Illinois, Indiana, and Ohio (figure 1).

Surveys of school children in Kansas City,[35] Texas,[38] and Iowa[39] have shown that the high rates in young adults are reflected by early acquisition of sensitivity. For example, in Kansas City where 60 to 70 per cent of young adults are reactors, a survey of school children[35] revealed specific age rates as follows: 5 per cent reactors at 0 to 2 years; 20 per cent at 2 to 6 years; 30 per cent at 6 to 8 years; 50 per cent at 8 to 12 years; and 65 per cent at 12 to 18 years.

Although these studies suggested strongly that histoplasmosis is a widely distributed pulmonary infection in man which often results in pulmonary calcification, the demonstration of benign nonepidemic clinical pulmonary infection in patients by Bunnell and Furcolow[40] and others[8,9,34,41–43] strengthened this concept. Christie[44] provided further support for the concept of minimum infections by demonstrating *H. capsulatum* in active interstitial lesions in the lungs of 4 infants dying from unrelated causes.

The conclusion that benign asymptomatic infection by *H. capsulatum* occurs commonly in the central United States is based in part on the assumption that the skin hypersensitivity to this fungus is quite specific. The specificity of the

dermal response to this antigen, however, has been questioned by several authors.[45–49]

Smith and associates[49] and others,[46,50] for example, pointed out certain cross reactions between histoplasmin and other fungus antigens, such as coccidioidin, blastomycin, and *Candida albicans*. In fact, the occurrence of borderline positive, occasional undoubted positive skin reactions to coccidioidin in certain individuals from the central United States strengthened Smith's[30] postulation that histoplasmosis was the cause of nontuberculous pulmonary calcifications in that area. There can be no doubt, however, that animals and man develop specific skin sensitivity to the antigen, histoplasmin, in a predictable manner with experimental[49] or natural infection.[51] Purification of the antigenic protein in the crude histoplasmin used currently for skin testing may help to resolve the problems resulting from nonspecific reactions.

In spite of the fact that a minor degree of cross reactivity between histoplasmin and the other fungus skin test antigens can be demonstrated, great practical significance cannot be attached to it[44] as the endemic areas of histoplasmosis and coccidioidomycosis do not overlap significantly, and sensitivity to blastomycin in most parts of the United States is extremely infrequent.

In addition to the skin test, serologic determination of circulating antibodies has been used more recently in the study and diagnosis of histoplasmosis. Precipitin reactions with several types of antigen have been demonstrated in the sera of rabbits hyperimmunized with histoplasmin[52] and of patients acutely ill with histoplasmosis.[53] Complement fixation studies[54–59] with whole yeast antigen, disrupted yeast-cell antigen, and mycelial-phase antigen have shown that experimental and natural infections are associated with antibody rises. These complement fixing antibodies are seldom demonstrable in asymptomatic skin-test reactors[60] and not predictably found in patients with mild illness.[53]

Repeated skin tests in persons reacting positively have been shown to result in a rise in complement fixing antibodies[62,63] when crude histoplasmin or ground yeast-phase antigens were used, but not when the intact yeast cells or mycelial-phase broth supernate are employed.[60] From data recently available,[53] it appears that the precipitin reaction is a more sensitive indi-

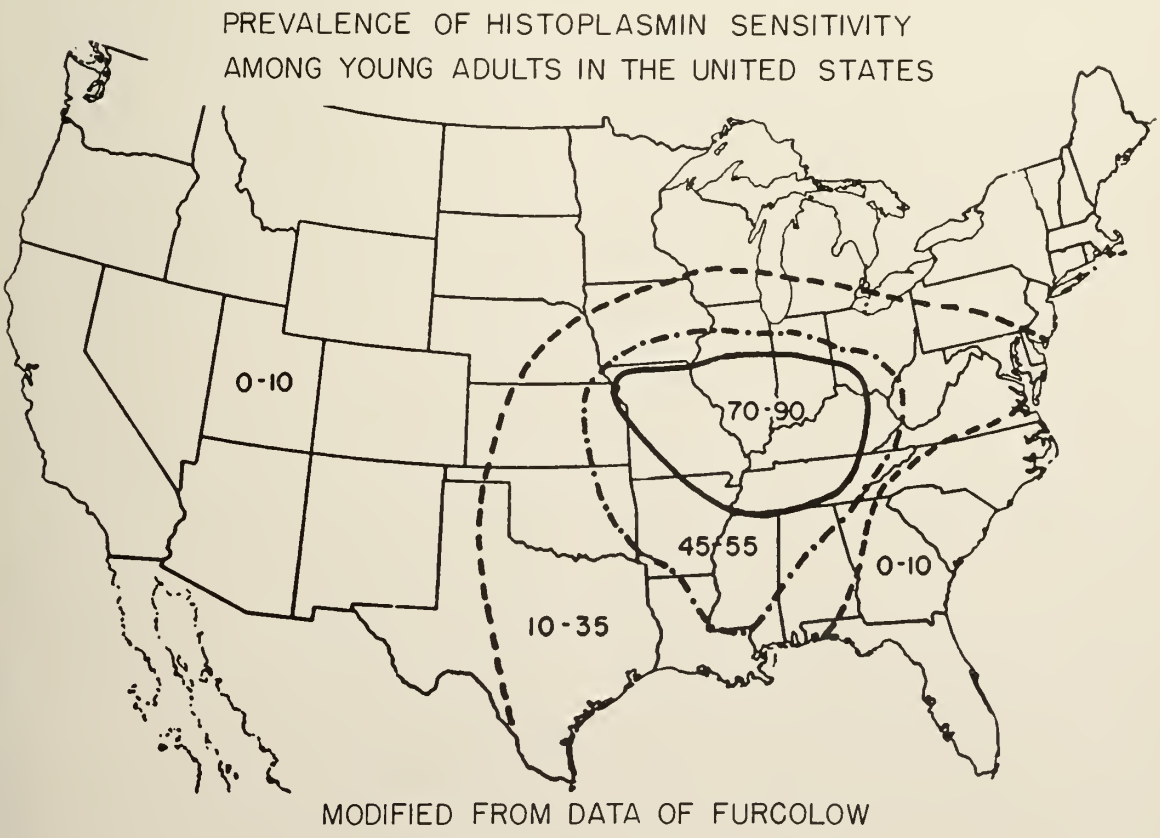

Fig. 1. Approximate rates of sensitivity to histoplasmin in young adults in the United States.

cator of the presence of active infection, although the complement fixing antibodies persist for a longer period of time. More information on this point is required before the relative value of the serologic tests in the human disease can be clearly established.

A hemagglutination test for circulating antibodies in hyperimmunized rabbits has been described by Norden,[61] but it has not been applied to the study of the clinical disease.

Some of the most crucial information on histoplasmosis as a clinical disease and on the ecology of the organism has come from the careful clinical and epidemiologic studies of epidemic outbreaks which have been reported by Loosli and associates[2,3] and by Furcolow and Grayston.[4,5]

White and Hill[64] were the first to demonstrate that a group of persons whose pulmonary illness resulted in disseminated calcification of the lungs had positive histoplasmin skin tests. However, the first epidemic thoroughly investigated during the illness of the patients was that reported by Loosli and collaborators[2,3] in which the etiologic agent was demonstrated both in the patient and at the environmental source[65] of his infection.

They studied 8 members of a farm family in northwestern Indiana, of whom 3 became severely ill within a short period of time. The symptoms in each instance included fever, chills, chest pain, cough, weight loss, and anorexia. In 1 patient, the illness was very severe and positive cultures were obtained from bone marrow and sputum. Infiltrations on the chest roentgenogram, the presence of complement fixing antibodies, and positive skin tests were found in all 3. In addition, 3 other members of the family developed roentgenogram changes, positive skin tests, and, in 2, elevated complement fixing antibody titers. Spores of *H. capsulatum* were isolated by direct microscopic examination and culture from the wall of an unused silo.[65] After this discovery, it was ascertained that the infected members of the family had been exposed to dust in this silo. Thus the etiology of the disease was firmly established, and the point source at which it was contracted was demonstrated.

Furcolow and Grayston[4,5] have also made important contributions to our current concepts of the epidemiology of histoplasmosis. They studied 13 epidemic outbreaks of histoplasmosis over a three-year period and found a point source of infection in 11. In several instances, the outbreaks of histoplasmosis were discovered when the authors looked into epidemics of pulmonic disease reported as "cave sickness," "angleworm pneumonia," miliary pneumonitis, and then reinvestigated the involved patients searching for the source of their infection. In each of the 13 epidemics, the illness was attributed to infection with *H. capsulatum* on the basis of skin test and serologic studies, and in 11 of the epidemics studied, isolation of the fungus from the point source. Although data obtained in retrospect showing that an illness of an individual patient has been histoplasmosis may be unconvincing, the evidence of the prior occurrence of infection with *H. capsulatum* in groups of patients with compatible epidemic disease who have been exposed to spores at a point source provides a strong case for an etiologic relationship.

Complement fixing antibodies were present in 53 out of 54 patients tested, and present in high titer in 44 patients. The frequency of healing by calcification in histoplasmosis, particularly in epidemics, was indicated by the fact that 63 of 113 persons developed calcifications. Of these, 44 developed typical nodular disseminated deposits. The authors were able to relate the severity of clinical disease to the degree and duration of exposure to the spores, and to show that the attack rate in persons exposed to a point-spore source is approximately 90 per cent. Acquisition of infection was usually associated with stirring up dust or handling dried or dusty fowl excreta. By demonstrating no secondary cases, they provided evidence that person-to-person transfer is not an important mode of acquisition of the infection. Rather, their studies contributed solid evidence that infection by *H. capsulatum*, a normally saprophytic fungus, is acquired accidentally through air or dust-borne spores. No clear relationship between a previously positive skin test and immunity to infection upon re-exposure to a spore source could be obtained.

A chronic pulmonary type of histoplasmosis unlike the epidemic form has been recognized recently. Monroe and Kurung[66] described 1 case, and Furcolow[67] observed 22 samples of chronic progressive caseous pulmonary disease with fibrosis and cavitation. Most of these patients were elderly, and have been shown to be tuberculin negative without acid-fast bacilli in the sputum. *H. capsulatum* has been repeatedly isolated from their sputum.

Hodgson and associates[9] reported the case of a patient in whom *H. capsulatum* was cultured from an isolated pulmonary nodule resected surgically, suggesting histoplasmosis as a necessary consideration in the differential diagnosis of the so-called "coin" lesion. Local forms of the disease, restricted to the mucous membranes of

the tongue, gums, pharynx, or larynx have been described[6,68] but appear to occur infrequently. Zinneman and Hall[68] have made careful studies of a man with this type of disease.

Laboratory and ecologic studies have, in recent years, expanded considerably our knowledge of the growth and sporulating characteristics of *H. capsulatum* in nature. Emmons[48,69] first used a flotation technic for concentrating the spores to isolate *H. capsulatum* from the soil. Shortly thereafter, Ajello and Zeidberg[70] and Furcolow and associates,[4,5] using Emmons' concentration technic, grew the fungus from the soil samples in the study of point sources of epidemics. Furcolow and Larsh[71] and Grayston and associates[65] isolated the microorganism directly from soil in their respective epidemic studies.

Survey of the prevalence of spores of *H. capsulatum* in the soil of rural Williamson County, Tennessee, an area in which 80 to 90 per cent of young adults are reactors,[72] yielded 11 positive cultures from 299 samples cultured. Isolations were made most frequently from areas in which poultry was housed and in which the soil was shallow, acid, and moist. As a part of this study,[73] it was shown that environmental conditions in regard to moisture around the homes of a large group of young children tested correlated roughly with the incidence of skin sensitivity to histoplasmin. These data, as they are germane to ours, are summarized in table 1.

TABLE 1
INFLUENCE OF TYPE OF HOMESITE ON HISTOPLASMIN SKIN SENSITIVITY

Environmental condition at homesite of persons tested	*Percent reactors*	
	Age under 5 years	*Total group*
Damp	87.5	87.2
Dry with creek	65.8	67.0
Dry	28.4	51.2

These observations were substantiated and extended by Menges and associates.[74] They found that growth of *H. capsulatum* in soil and on elm bark was optimum at 25 to 30° C. and required 100 per cent humidity. It failed to grow when the humidity was reduced even slightly below 100 per cent or the temperature below 20° C. In addition, evidence was obtained that prolonged exposure to temperatures between 40 to 50° C. is destructive to spores.

Larsh and associates[75] attempted to improve the recovery of spores from contaminated soils by a technic of inoculating mice with 1 to 10 dilutions of the suspected soil containing antibiotics. The mice are sacrificed two to four weeks later, and spleen tissue inoculated onto Sabouraud's glucose agar. The finding of Ajello and Runyon[76] that mice can be infected with a single spore makes this seem an ideal method for isolating the fungus. However, the small inoculum of soil tolerated by the mice limits the usefulness of the method.

The concept that *H. capsulatum* is air-borne to man from saprophytic forms of the fungus in the environment has received support in recent studies which show that the spore is usually less than 5μ in diameter,[77,78] compatible with air-borne spread, and that it can be isolated from naturally contaminated air.[79]

Other laboratory studies of interest have appeared recently. It has been shown that *H. capsulatum* can be grown in explants of infected splenic tissue,[80] and that Earle's L-strain of mouse fibroblasts supports intracellular multiplication of the yeast.[81] Kipkie and Howell[82] and Menges and associates[83] have studied the histopathology of experimental histoplasmosis in mice, finding predominant involvement of the liver and spleen. Grayston and Altman[84] have demonstrated that in experimental histoplasmosis in mice, infection could be accomplished easily by intranasal or intraperitoneal routes using small numbers of spores, but only with extremely large numbers, if at all, when the spores were given orally.

Treatment of this disease has been unsuccessful; all antibiotics have been used without effect. Christie and associates[85] studied ethyl vanillate, a phenol derivative with potent in vitro activity, as a possible therapeutic resource in children with the disseminated form of the disease. Although their early results were very encouraging, there have been few reports[86,87] elsewhere to suggest that this drug is effective in vivo. Zinneman and Hall's[68] patient responded favorably to the drug, relapsed later, and responded again to therapy. Saslaw and MacMillan[88] have very recently reported studies in which mice infected with *H. capsulatum* were given large doses of ethyl vanillate by gavage. In spite of adequate blood levels achieved, no difference in mortality from similarly infected controls could be demonstrated.

Histoplasmosis has not been an unknown disease in Minnesota. As previously cited,[18] the first reported case in this country was in a Minnesota woman from the Lake Minnetonka area. Iams and associates[11] reported an infant born in St. Paul who developed, in the first month of life, a disease recognized at autopsy as disseminated histoplasmosis. Other cases recognized in the state and reported to the State Board of

TABLE 2

HISTOPLASMOSIS IN MINNESOTA

CASES REPORTED TO HEALTH DEPARTMENT 1926-1953

Year	*County*	*Age*	*Outcome*
1926	Hennepin	52	died
1945	Ramsey	2 mo.	died
1948	Detroit Lakes	28	lived
1948	Detroit Lakes	35	lived
1948	Detroit Lakes	45	lived
1948	Detroit Lakes	71	lived
1948	Detroit Lakes	77	lived
1948	Detroit Lakes	80	lived
1948	Detroit Lakes	—	lived
1948	Hennepin	77	died
1949	St. Louis	36	lived
1951	Dakota	56	lived
1951	Hennepin	11	lived
1951	Hennepin	31	lived
1951	Redwood	26	lived
1951	St. Louis	19	lived
1951	Wabash	13	lived
1952	Hennepin	30	lived
1952	St. Louis	31	lived
1953	Hennepin	31	lived
1953	Renville	35	lived
1953	Hennepin	70	died

Health up to 1953 are listed together with their age and county of origin in table 2. Information in the table was kindly supplied by Dr. C. B. Nelson of the State Health Department. It is perhaps significant in view of findings reported in this paper that all 3 of the fatal cases reported in adults lived in the Lake Minnetonka area and one-third of the cases occurred in persons from Hennepin County.

Zinneman and Hall's[68] patient lived in Duluth, Minnesota all of his life except for service in North Africa and Italy during World War II.

Histoplasmosis was recognized in retrospect[5] as the cause of an unusual outbreak of pulmonary disease involving 6 members of a Detroit Lakes farm family in January 1948.[89] This illness was described as severe, requiring hospitalization of 4 members of the family. All had disseminated pulmonary lesions demonstrable by roentgenograms. Reinvestigation by Grayston in 1951 showed all to have a positive histoplasmin skin test. Soil taken from beneath the kitchen floor yielded *H. capsulatum* on culture.

No similar outbreaks have been reported in Minnesota. Two examples of symptomatic disseminated pulmonary disease with positive histoplasmin skin tests and complement fixation titers, several examples of disseminated nodular pulmonary calcifications in patients with positive histoplasmin skin tests, and 1 unreported fatal case of disseminated systemic histoplasmosis in an adult have come to the attention of the author during the year in which the studies reported herein were conducted. In addition, 1 example of fatal systemic histoplasmosis in a dog observed by the author may be added to the single case referred to by Zinneman and Hall.[68]

Current information on reactivity to the histoplasmin skin test among lifelong residents of Minnesota is derived from several sources. Palmer's[33] survey of 937 "lifetime resident" student nurses showed that 38 or 4.1 per cent were positive reactors. Smith and associates[49] reported 3 reactors in 90 tested or 3.3 per cent; Loosli and associates[90] found 22 or 10 per cent reactors among 220 college students who grew up in Minnesota. Myers,[91] studying about 1,300 University of Minnesota students in 1947 and 1948, found that less than 1 per cent of students from the northwestern part of the state reacted to histoplasmin whereas up to 10 per cent of those from the southeastern regions reacted.

Iams[37] tested a sample of 210 hospitalized children from Minneapolis and surrounding areas and found 1 per cent reactors. He quotes J. W. Johnson of Minneapolis as finding 40 reactors or 8 per cent out of 500 persons tested in Minneapolis. Troxell[92] has shown what he considered an unexpectedly high percentage of reactors to histoplasmin in a group of patients at Hastings State Hospital who were known by roentgenograms to have pulmonary calcifications; 39.9 per cent reacted to histoplasmin while 96 per cent reacted to tuberculin.

CLINICAL STUDIES

The clinical[93] and epidemiologic[94] studies to be reported began on August 27, 1953, when a 4-year-old Wright County farm boy, referred to the University of Minnesota hospitals, was found to have disseminated histoplasmosis by morphologic, serologic, and cultural studies of the bone marrow and blood. It was learned at the same time that this child's 2½-year-old sibling had unexplained pulmonary disease of three-months' duration. Serologic studies and skin tests indicated that his illness also was due to infection with *H. capsulatum*.

It was subsequently learned that 6 adult mem-

Fig. 2. Illustrative chest roentgenograms of persons involved in family outbreak of histoplasmosis, 1949-1953. (*a*). Case 1, D. H. Roentgenogram taken seven days after onset of illness: negative. (*b*). Case 1, D. H. Ten days later. Note diffuse bilateral infiltrations. (*c*). Case 2, A. H. Taken June 16, 1953, during height of illness. Bilateral hilar enlargement and peribronchial infiltration are present, with a pneumonic infiltration in the left upper lobe subtended by an enlarged lymph node. (*d*). Case 3, C. H. Taken February 25, 1949, during acute pulmonary illness. Note bilateral hilar infiltrations and diffuse interstitial pneumonitis. Present chest roentgenogram shows hilateral hilar calcifications. (*e*). Case 4, L. H. Taken April 27, 1953. Shows end result of a diffuse miliary infiltrative process occurring in 1949. Note multiple parenchymal nodular calcifications characteristic of histoplasmosis. (*f*). Case 5, M. H. Taken May 29, 1954. Shows multiple parenchymal nodular calcification resulting from acute process in 1949.

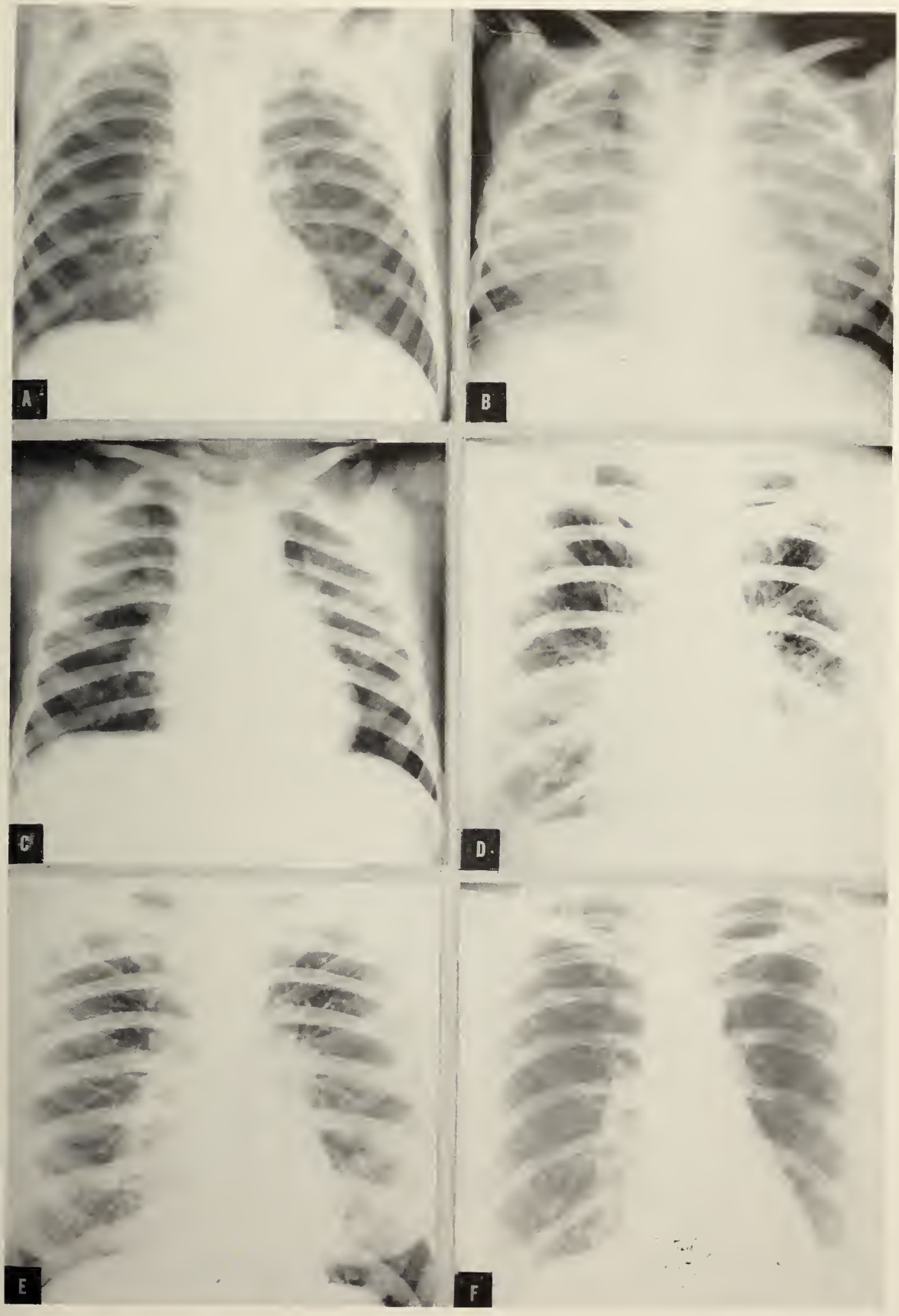
A
B
C
D
E
F

TABLE 3

SUMMARY OF CASES

MAPLE LAKE HISTOPLASMOSIS OUTBREAK, 1949-1953

First initials	*Age*	*Sex*	*Date of onset*	*Symptoms*	*Duration*	*Calcification on chest x-ray*	*Histoplasmin skin test*	*Complement fixation Test*
DH	4	M	Aug. 22, 1953	Fever, sweats, weight loss, hepatosplenomegaly, positive bone marrow, died.	4 weeks	–	–	1-80*
AH	2½	M	June 4, 1953	Cough, fever, malaise, erythema multiforme, negative bone marrow	8 weeks	+	+	1-32*
CH	28	M	Feb. 23, 1949	Cough, fever, chills, chest pain, prostration, severely ill	6 weeks	+	+	neg.
LH	27	F	Feb. 22, 1949	Cough, fever, chills, malaise, severely ill	8 weeks	+	+	1-8
MH	55	F	Feb. 18, 1949	Fever, chills, nausea, severely ill	4-5 wks.	+	+	neg.
TH	58	M	Feb. 18, 1949	Cough, fever, malaise, mild illness	4-6 wks.	–	+	1-8
RH	24	M	Feb. 23, 1949	Cough, fever, malaise, mild illness	1-2 wks.	+	+	neg.
BH	55	M	Feb. 23, 1949	Fever, malaise, cough	2 weeks	+	+	neg.

*Both of these complement fixation tests performed during or shortly after illness. The others were performed on serum collected in October, 1953

bers of this family had a simultaneous pulmonary disease of varying degrees of severity during February 1949. The onset of illness in these 6 persons could be dated within the same five-day period. Retrospective evaluation of serial chest roentgenograms, skin-test reactions, and serologic data suggest strongly that their disease was epidemic pulmonary histoplasmosis.

The clinical aspects of illness and laboratory studies in each of the 8 affected members are summarized in table 3. Illustrative chest roentgenograms are shown in figure 2.

It will be seen from table 3 that the severity of illness in the 1949 outbreak varied greatly in individual patients. Symptomatology ranged from mild respiratory manifestations to severe incapacitating systemic disease with pulmonary manifestations in 3 persons requiring hospitalization (C.H., L.H., and M.H.). These 3 patients had almost identical illnesses featured by sudden onset of fever, chilly sensations, aching pains, progressively severe cough, and dyspnea, accompanied by severe sweating, weight loss, and prostration. Physical findings in each were minimal and consisted of only a few inconstant rales in both lung fields. Demonstration by roentgenograms of parenchymal and hilar infiltrations in each of these patients at the time of their illness provided a basis for the clinical diagnosis of atypical pneumonia (figure 2*d*). Each had a prolonged illness lasting two to eight weeks and recovery was slow. Residual calcifications are present in each of the patients except T.H. Both L.H. and M.H. have multiple nodular calcifications on chest roentgenograms at the present time (figure 2*e* and *f*).

Each of the patients involved in the 1949 outbreak has a positive histoplasmin skin test. Complement fixation tests, performed through the courtesy of Dr. S. B. Salvin, U.S.P.H.S., Rocky Mountain Laboratory, Hamilton, Montana, on specimens drawn in October 1953, were positive in 2 out of the 6 patients, while the precipitin test on the same serum specimen was negative in each instance.

The illness of D.H. was acute disseminated histoplasmosis. He came to the hospital after one week of fever of undetermined origin. Shortly after admission, the yeast forms of *H. capsulatum* were found in the macrophages in his bone marrow. A photomicrograph taken from the original smear is shown in figure 3*a*. The course of his illness was characterized by progressive hepatosplenomegaly, high spiking fever, anemia, leukopenia, and thrombopenia.

The organisms were cultured from both the blood and bone marrow. Ethyl vanillate therapy in amounts adequate to achieve high blood levels was without avail, and the child expired two weeks after admission to the hospital. Since no postmortem examination was obtained in this patient, a photomicrograph illustrating the typical histopathology of the disseminated form of the disease in another patient is shown in figure 3*b*. Here *H. capsulatum* yeast forms are seen packed into the Kupffer cells of the liver in large numbers. Failure to demonstrate histoplasmin skin sensitivity in D.H. may be explained on the basis of the overwhelming nature of the infection; a negative skin test under these circumstances has been reported previously.[95] However, in spite of the negative skin test, a high titer in complement fixing antibodies to histoplasmin was observed.

The illness of A.H. is interpreted to represent pulmonary histoplasmosis. His illness was characterized by fever, cough, slight loss of weight, erythema multiforme-type rash, and pronounced

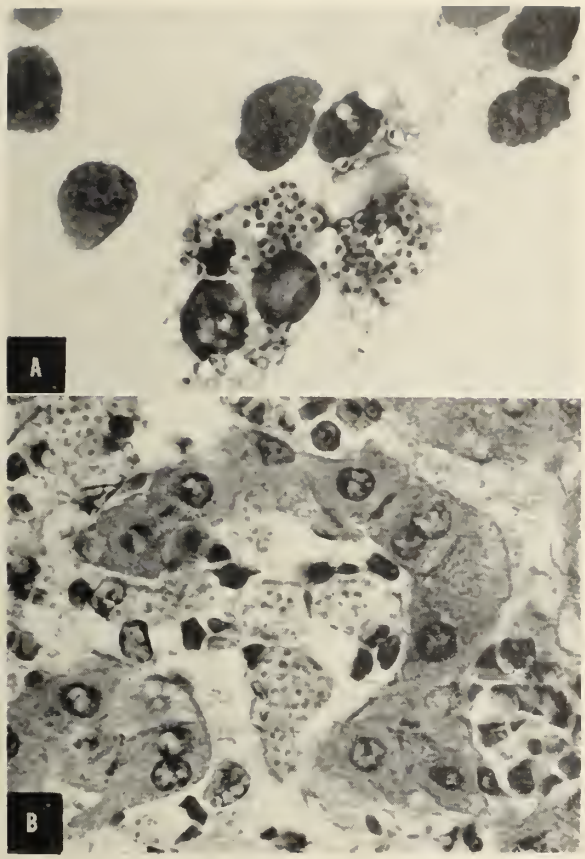

Fig. 3*a*. Bone marrow smear taken from case 1 (D. H.) during life, showing numerous yeast forms of *H. capsulatum* engorging macrophages. Wright-Giemsa stain x 1,200. (*b*). Illustration of histopathology of histoplasmosis. Section of liver taken from a 71-year-old man dying of generalized histoplasmosis showing engorgement of Kupffer cells with yeast form of *H. capsulatum*. Hematoxylin-eosin stain x 1,000.

loss of vigor. Serial chest roentgenograms over the eight-week period of illness demonstrate the evolution of a diffuse bilateral pulmonary process and increased hilar shadows, particularly on the left where there were parenchymal infiltrations extending into the left upper lobe. The parenchymal process resolved during convalescence; hilar calcification is now present. A positive histoplasmin skin test was demonstrated three months after onset. Complement fixing antibodies were present in high titer at the same time. Sternal bone marrow failed to yield *H. capsulatum* on smear or culture.

Interpretation of the 1949 group of cases as examples of epidemic histoplasmosis depended upon demonstration of progression of typical roentgenogram changes in L.H. and M.H., the fact that all now have positive skin tests, and that 2 still have positive complement fixation tests. The disseminated nodular calcifications demonstrated as the end result of the 1949 illness in L.H. and M.H. are characteristic of histoplasmosis.[1,5,64] Because *H. capsulatum* was not isolated from any patient in the first epidemic, it must remain presumptive that the original illness was histoplasmosis.

In addition to the cases indicated in table 3, there were 4 other members of this family involved in the cleaning and rebuilding process around the farm during early 1949, who recall having flu-like illnesses at about the same time. In none of these persons was it possible to determine with certainty that the illness coincided with the others. However, these 4 persons have positive histoplasmin skin tests and demonstrable pulmonary calcifications at the present time. Two members of this family, not previously described, have been in tuberculosis sanatoriums because of pulmonary disease. At no time was a positive tuberculin test demonstrated, or have tubercle bacilli been isolated from the sputum. At the present time both have a positive histoplasmin skin test. A cousin of the affected siblings was observed to have a mild illness characterized by low-grade fever and listlessness during the course of the epidemic investigation in October of 1953. At that time a histoplasmin skin test was negative and attempts to isolate *H. capsulatum* from the bone marrow and blood were unsuccessful. However, on a repeat skin test in May 1954, he was found to be a strong reactor to histoplasmin. No evidence of pulmonary disease could be detected from roentgenograms.

Many of the reported epidemics of histoplasmosis have resulted from simultaneous exposure of a group of people to a concentrated source of spores.[2–5] Therefore, inquiry was made into occurrences at the time of onset which might implicate a site or sites in the area as a source of infectious spores.

The first group of cases occurring in February 1949 involved most of the adults then closely connected with the family. Illness in each occurred shortly after they established residence at the present farm location and during the cleaning-up process which was necessary to prepare the farmhouse and barns for occupation. Efforts to recall a single occasion on which the entire group might have had a single massive contact with a source of spores during the two-week period just preceding onset of illness have been unsuccessful. The areas which were cleaned, however, were said to be extremely dusty. It was remembered that on several occasions large amounts of dust were stirred up in rooms in which all members of the family were working. It is interesting that the outbreak occurred during the winter when there was snow

12 inches deep on the ground. The women in the family went to the barns or other outlying buildings only occasionally and never as a group. On the other hand, the farmhouse was the scene of many gatherings of all of these persons. Therefore, it seems probable that the source of infection probably was in or around the house.

It is doubtful whether the illness of the 2 boys, D.H. and A.H., which occurred in 1953, can be related to a single exposure to spores, as the exact time of onset of illness in D.H. could not be determined. A particular incident deserves mention. A short time before the onset of fever in A.H., the boys were playing in a barn when a large amount of old hay suddenly fell upon them covering them with a great cloud of dusty hay. Cultures of material from the site of this event taken six months later were negative for *H. capsulatum*.

All attempts thus far to isolate the fungus from the vicinity of the farm site have been unsuccessful. Over 50 samples have been cultured by the technic of Larsh and associates.[75] Further studies are in progress in an attempt to demonstrate a point source of spores which is thought to exist somewhere on this farm.

EPIDEMIOLOGIC STUDIES

Epidemiologic studies of this outbreak had two objectives; first, to determine the incidence of positive skin reactors in the immediate area of the site of the outbreak; and second, to determine the prevalence of skin test reactivity throughout Wright County, Minnesota, in which this epidemic occurred.

Preliminary survey. The initial epidemiologic studies were made at Maple Lake, October 3, 1953. At that time, approximately 100 volunteers gathered on the farm for skin tests. These volunteers included most people living on surrounding sections. In addition, a few residing some distance away participated in the testing program. Skin tests were performed with standard antigen (lot H-KC-5, U.S.P.H.S. Laboratories, Kansas City, Kansas). Readings were made forty-eight hours after application of the skin tests. Results of these tests are presented in table 4, which show that there were 26.3 per cent reactors among 76 persons on whom information was sufficient to establish the degree of previous contact with the site of the outbreak. Too few persons were tested to provide reliable information on age or sex distribution of the reactors. Arranged on a basis of previous contact with the site of the outbreak, the data indicate a difference between two groups of persons. Only 10.8 per cent of those tested who had never been on the premises reacted to the skin test, whereas 50 per cent of those who visited or worked there at some time during the previous four years were reactors. Although it is not shown, positive reactions were found in 75 per cent of persons who had more than casual contact with the farm site in that they had worked repeatedly on the farm during the previous four-year period.

TABLE 4

RELATIONSHIP BETWEEN EXPOSURE TO SITE OF OUTBREAK AND PRESENT SKIN SENSITIVITY TO HISTOPLASMIN

Exposure history	*No. tested*	*No. positive*	*Per cent positive*
Never on premises	46	5	10.8
Visited or worked	30	15	50.0
Total	76	20	26.3

These data suggest a relationship between prior contact with the site of the epidemic and the present status of skin test, and indicate further that the farm or buildings are a probable source of infectious spores.

Wright County survey. The preliminary skin test survey cited above gave distinctly surprising results in view of the previously reported low incidence of histoplasmin reactors in the state of Minnesota.[33,90,91] Therefore, it seemed desirable to conduct a more extensive survey, which, by utilizing accurate sampling methods, would provide reliable information on the prevalence of sensitivity in Wright County. Accordingly, arrangements were made to survey all the public and parochial schools within the geographic limits of Wright County. Approximately 85 per cent of children attending these schools were tested. The remaining 15 per cent were not included either because parents denied permission, or because of absence on the day of testing or the day of reading. The tests were performed by injecting intradermally histoplasmin (Kansas City CDC lot H-KC-5) and tuberculin (PPD-S, 0.0001 mg. per test), 0.1 cc. in opposite forearms. Reading of the test was made forty-eight hours

TABLE 5

RESULTS OF HISTOPLASMIN AND TUBERCULIN SKIN TESTS IN ALL CHILDREN AND ADULTS INCLUDED IN THE WRIGHT COUNTY SURVEY, MAY 1954

Skin test antigen	*No. tested†*	*No. positive**	*Per cent positive*
	Children		
Histoplasmin	5,487	407	7.5
Tuberculin	5,487	68	1.2
	Adults‡		
Histoplasmin	199	38	19.1
Tuberculin	192	49	25.5

†86 per cent of 6,411 children enrolled were tested.
*3 children and 6 adults reacted to both antigens.
‡School teachers, principals, and custodial workers at the various schools surveyed.

after application; a positive test was interpreted as one in which more than 5 mm. of induration could be detected at the site of injection. A 14x17 inch chest roentgenogram of every person reacting to either of the test antigens was obtained.

The raw data on skin-test reactors to histoplasmin and tuberculin are presented in table 5. These data show that of 5,487 children who were tested with both antigens, 407 or 7.5 per cent were positive reactors to histoplasmin, whereas only 68 or 1.2 per cent were tuberculin reactors. During this survey, 199 adults were tested, consisting chiefly of the school teachers, principals, and custodial workers at the various schools surveyed. Of the adults tested, 38 or 19.1 per cent were positive histoplasmin reactors and 25 per cent were tuberculin reactors.

The raw data on histoplasmin tests were sorted to exclude all but lifetime residents of Wright County. By definition, lifetime residence consisted of the individual living 80 per cent of his life within the geographic limits of the county. For the tuberculin rates, data shown include both lifetime and nonlifetime residents. Table 6 gives the specific age rates for histoplasmin and tuberculin reactors among the school children tested. It shows there was an increase in the incidence of reactors to histoplasmin from 3.4 per cent in the 5- to 6-year-old age group, to 11.2 per cent in the 17- to 18-year-old group. The over-all percentage of reactors in lifetime residents was 7.8 per cent. On the other hand, the tuberculin rates increased from 0.4 per cent to only 2.2 per cent, the maximum value in the 15- to 16-year-old age group. The over-all incidence of tuberculin reactors in the entire group was 1.1 per cent. It is evident from the data that the histoplasmin sensitivity rate for any given age group is approximately 5 times that of the tuberculin rate. This data is depicted graphically in figure 4. The gradual increase in the incidence of sensitivity to histoplasmin is clearly shown.

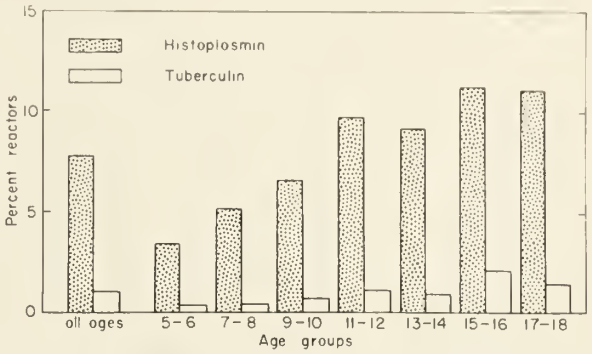

Fig. 4. Bar graph comparing age specific histoplasmin and tuberculin reactor rates among Wright County school children in 1954. Shaded bars represent the percentage of histoplasmin reactors in the age group. Open bars represent tuberculin reactors.

The adult rate of 19.1 per cent as shown in table 5 is somewhat higher than a rate which might be predicted for adults by extension of the curve described by this data.

Table 7 gives an indication of geographic variations in the prevalence of histoplasmin skin sensitivity among farm dwellers in various townships of Wright County. It may be seen that 2 townships have rates greater than 20 per cent, while 5 were between 10 and 20 per cent. In contrast, 4 townships had no positive reactors. These data have additional significance when they are plotted on a township map of Wright County as shown in figure 5. This map indicates clearly that histoplasmin reactors among farm dwellers are concentrated in the southeast corner of the county. This area borders western Hennepin County and is immediately north and west of Lake Minnetonka. It is of interest that the majority of patients reported to have fatal histoplasmosis in the state of Minnesota (table 2) lived in the area west of Lake Minnetonka. A survey such as this would be of value in western Hennepin County and the area around Lake Minnetonka.

Conditions of humidity are known to affect the growth of *H. capsulatum* in nature as well

TABLE 6

PREVALENCE OF TUBERCULIN AND HISTOPLASMIN SENSITIVITY AMONG SCHOOL CHILDREN OF WRIGHT COUNTY, MINNESOTA, BY AGE

Test antigen		*Age last birthday*							
		5-6	*7-8*	*9-10*	*11-12*	*13-14*	*15-16*	*17-18*	*Total*
Histoplasmin*	No. tested	277	819	712	704	566	485	286	3949
	No. positive	13	42	48	68	52	55	32	310
	% positive	3.4	5.1	6.7	9.7	9.2	11.3	11.2	7.8
Tuberculin	No. tested	484	1071	992	993	830	744	427	5541
	No. positive	2	5	8	13	10	16	7	61
	% positive	0.4	0.5	0.8	1.3	1.2	2.2	1.6	1.1

*Nonlifetime residents of Wright County were excluded in tabulation of histoplasmin sensitivity.

TABLE 7

PREVALENCE OF HISTOPLASMIN SKIN SENSITIVITY AMONG FARM DWELLING SCHOOL CHILDREN OF WRIGHT COUNTY, MINNESOTA, BY TOWNSHIP OF RESIDENCE*

Township	*No. tested*	*No. positive*	*Per cent positive*
Albion	163	4	2.5
Buffalo	105	15	14.3
Chatam	77	0	0.0
Clearwater	64	2	3.1
Cokato	93	2	2.2
Corinna	89	4	4.5
Frankfort	145	19	13.1
Franklin	131	39	29.8
French Lake	114	0	0.0
Maple Lake	77	6	7.8
Marysville	119	13	10.9
Middleville	106	11	10.4
Monticello	110	4	3.6
Ostego	76	1	1.3
Rockford	112	29	25.9
Silver Creek	108	6	5.6
Southside	54	0	0.0
Stockholm	97	0	0.0
Victor	92	4	4.3
Woodland	78	13	16.7
Total	2,010	172	8.6

*Only farm dwelling lifetime residents of Wright County who have lived on their present farms for at least five years are included in this tabulation.

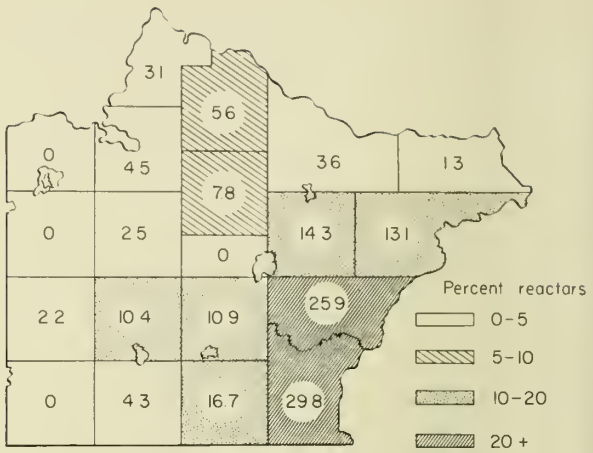

Fig. 5. Prevalence of histoplasmin skin sensitivity, Wright County, Minnesota, 1954. Shows geographic distribution of reactors to histoplasmin among farm-dwelling Wright County school children who have resided at their present farm location at least five years. It is evident the majority of reactors are concentrated in the southeastern corner of the county. This area borders western Hennepin County and is immediately west and north of Lake Minnetonka.

as in vitro.[73,74] It was of interest, therefore, to inspect this map for any differences in topography in terms of lakes, rivers, or elevations which might account for the striking geographic distribution of reactors. However, no gross correlation between the natural sources of water or moisture, and the existence of skin sensitivity to histoplasmin could be found.

The data were then tested for differences in the incidence of sensitivity among children who had lived on a farm most of their lives, and those who had lived in a village most of their lives. There are no towns with a population greater than 2,000 in Wright County. For purposes of this analysis, data on children who had lived on their present farm or in their present village location for the past five years were reviewed. The incidence of reactors by age group in these two categories is given in table 8. There is a significant difference in the incidence of reactors among farm and village dwellers of all ages. The incidence in the youngest age groups is approximately equal, but among the older children differences are clearly shown. Figure 6 depicts graphically this relationship between the type of residence and the incidence of histoplasmin sensitivity. It may be inferred from these data that children of rural origin probably have had more intimate or repeated exposure to the fungus than those living in villages. This finding is similar to that of Prior and Allen[96] and Furcolow and Sitterley[97] who studied populations in Ohio and Kansas, respectively.

In an attempt to confirm the impression gained during the survey that histoplasmin reactors were concentrated in family groups, the data were arranged as indicated in table 9. Households were grouped by the number of children in each household and by the number of households with a given number of reactors to histoplasmin. In order to evaluate the resultant figures, the frequency to be expected theoretically

TABLE 8

INFLUENCE OF TYPE OF RESIDENCE ON PREVALENCE OF HISTOPLASMIN SKIN SENSITIVITY AMONG SCHOOL CHILDREN OF WRIGHT COUNTY, MINNESOTA*

Type of residence		*Age last birthday*							
		5-6	*7-8*	*9-10*	*11-12*	*13-14*	*15-16*	*17-18*	*Total*
Farm (rural)	No. tested	205	492	459	433	350	300	146	2385
	No. positive	6	27	34	46	36	41	19	209
	% positive	2.9	5.5	7.4	10.6	10.3	13.7	13.0	8.8
Village (urban)	No. tested	172	327	753	271	216	185	140	1564
	No. positive	7	15	14	22	16	14	13	101
	% positive	4.1	4.6	5.5	8.1	7.4	7.6	9.3	6.5

*Only lifetime residents of Wright County who have lived in their present situation for at least five years are included.

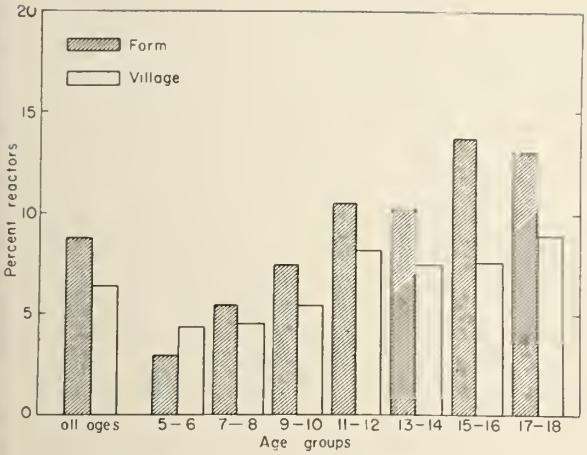

Fig. 6. Bar graph showing effect of the type of residence. Comparison is made of the incidence of reactors to histoplasmin among school children of Wright County who have lived on a farm and a similar group who have lived in a town at least five years.

was computed by the binomial expansion method. It is seen that certain differences exist in the expected and the observed number of households with each number of reactors. Of 1,080 households studied, 921 were found to have no reactors against an expected value of 892. On the other hand, among those families in whom 2 children were reactors, 16 were observed where only 10 were expected, and among those with 3 members in the household reactors, 8 were observed where none would be expected to occur by chance alone. A family which was not included in the tabulation was found to have 7 reactors among 7 children tested. From these data, it may be inferred that many families in Wright county are exposed to a source of spores in their immediate environment.

By plotting the data on families of reactors in the three townships of highest prevalence, distribution of reactors can be shown to be extremely irregular. A farm on which several reactors are living is surrounded by several in which there are no reactors. This seemed to be true particularly in Maple Lake Township, the site of the epidemic outbreak previously described, suggesting that the organism infects human beings by exposure in highly restricted areas rather than by widespread air-borne dust.

The incidence of pulmonary calcifications among histoplasmin and tuberculin reactors found in the survey is presented in table 10. This table includes data on all children reacting to either antigen regardless of duration of residence. A small number of the roentgenograms were technically unsatisfactory and, therefore, were not included in the tabulation. From the table, it is seen that the percentage of histoplasmin reactors having pulmonary calcification is similar in each of the age groups, averaging 26.2 per cent for all ages. On the other hand, the incidence of pulmonary calcifications among reactors to tuberculin is considerably lower, although the figures are not as significant because of the smallness of the numbers. These data indicate that a given child with pulmonary calcification in Wright County is more apt to have had previous histoplasmosis than to have had tuberculosis. It is interesting, in addition, that roentgenograms in several histoplasmin-positive, tuberculin-negative children found in the survey show typical Ghon-type complexes which could as easily have been interpreted as evidence of previous primary tuberculosis. One of these roentgenograms is shown in figure 7*a* which represents a tuberculin-negative, histoplasmin-positive 10-year-old asymptomatic child with parenchymal calcifications in the left lung subtended by a calcified node. Among histoplasmin reactors, 22 children had x-ray findings of enlarged lymph nodes or parenchymal infiltrations suggesting more active processes. An example of this type of lesion is shown in figure 7*b*. Here

TABLE 9

HOUSEHOLD DISTRIBUTION OF FARM DWELLING HISTOPLASMIN SENSITIVE SCHOOL CHILDREN, OF WRIGHT COUNTY, MINNESOTA, 1954

Number of children in household	*Number of households with given number of reactors in household**														
	0		*1*		*2*		*3*		*4*		*5*		*6*		*Total*
	Obs+	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	*Obs*	*Exp*	
1	458	463	49	44	—	—	—	—	—	—	—	—	—	—	507
2	468	456	30	48	8	2	—	—	—	—	—	—	—	—	306
3	114	110	19	31	4	3	7	0	—	—	—	—	—	—	144
4	60	47	4	17	3	3	0	0	0	0	—	—	—	—	67
5	13	11	2	5	1	1	1	0	0	0	0	0	—	—	17
6	8	5	1	3	0	1	0	0	0	0	0	0	0	0	9
All households	921	892	105	148	16	10	8	0	0	0	0	0	0	0	1,080

*Number of households of lifetime, farm-residents living five or more years on their present farm, in whom the indicated number of reactors was found.

+Obs—observed number of households with given number of reactors.
Exp—expected number of households with given number of reactors. Determined by binomial expansion using a 7.8% basic sensitivity rate for purposes of computation.

TABLE 10

INCIDENCE OF PULMONARY CALCIFICATION AMONG TUBERCULIN AND HISTOPLASMIN REACTORS WRIGHT COUNTY SCHOOL CHILDREN, 1954

Age group	SKIN TEST POSITIVE*												Totals
	Histoplasmin				Tuberculin				Both				
	X-ray pos.	X-ray neg.	Total	% pos.	X-ray pos.	X-ray neg.	Total	% pos.	X-ray pos.	X-ray neg.	Total	% pos.	
5-6	3	10	13	23.0	0	2	2	—	0	0	0	—	15
7-8	13	37	50	26.0	1	2	3	—	0	1	1	—	54
9-10	14	52	66	21.2	0	9	9	—	0	0	0	—	75
11-12	23	61	84	27.4	1	10	11	—	0	2	2	—	97
13-14	14	44	58	24.1	3	6	9	—	1	0	1	—	68
15-16	28	58	86	32.6	3	14	17	—	1	3	4	—	107
17-18	10	34	44	22.9	2	6	8	—	0	0	0	—	52
Totals	105	296	401	26.2	10	49	59	16.9	2	6	8	—	468

*Includes all children reacting to either antigen regardless of duration of residence, who had followup 14″ x 17″ 6′ chest films satisfactory for reading.

†Pos. indicates presence of calcification on chest x-ray. Neg. indicates absence of calcification.

are seen bilateral hilar infiltrations and a large node on the right in a tuberculin-negative, histoplasmin-positive 13-year-old boy.

DISCUSSION

The view that histoplasmosis was a rare, fatal, disseminated fungus infection was widely held and universally taught until 1945. Through the efforts of several groups of workers between 1945 and 1950, this idea has undergone complete revision, resulting in the concept that histoplasmosis is a common, benign infection occurring in most parts of the central United States. With increased appreciation of the prevalence of this fungus disease, clinical and epidemiologic studies have revealed several clinical forms of infection not previously recognized.

With the accumulation of this newer knowledge, several attempts have been made to classify the clinical spectrum of histoplasmosis in humans.[13,42,44] The information presented in table 11 represents the author's effort to bring together and to classify clinical histoplasmosis as it has been described in the literature, yet to preserve the concept of a spectrum of manifestations.

In this table are listed clinical types of histoplasmosis separated on a basis of severity of symptomatology and chronicity, with indication for each type of the organ involvement usually

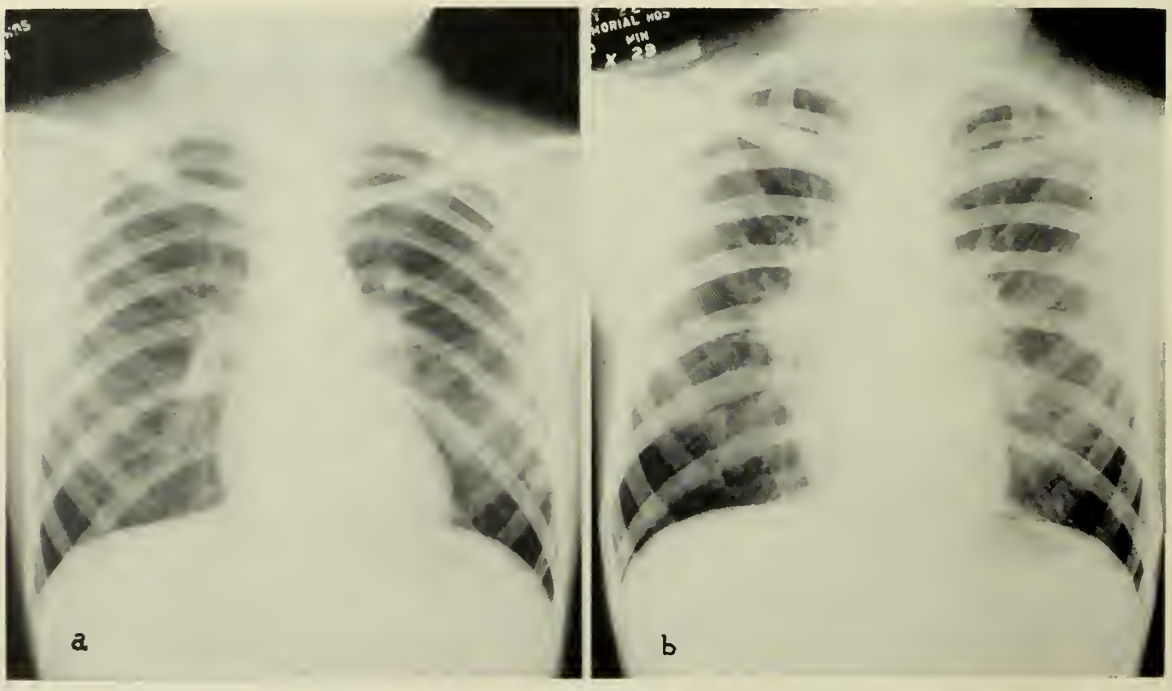

Fig. 7. Chest roentgenograms from 2 histoplasmin-positive, tuberculin-negative school children taken during the Wright County Survey, May 1954. Both of these children were asymptomatic and had no history of pulmonary disease. (*a*). Note parenchymal calcification subtended by a calcified node, suggesting a Ghon lesion. (*b*). Bilateral infiltrations in a large hilar node on the right.

encountered, the age of maximum incidence, the relative frequency, outlook, and laboratory data which support the diagnosis. Source references for each category are given. To indicate a span of severity, the disseminated form has been placed at one end of the spectrum, while asymptomatic acquisition of skin hypersensitivity is placed at the other. This order also indicates roughly the relative frequency of the various forms. Although most patients found to have histoplasmosis may be classified as suggested in the table, some will fit in no category, some perhaps in several of the suggested categories. Undoubtedly, the apparent gaps will be filled as other forms of this disease are described.

The results of investigation of the Maple Lake epidemic illustrate well this broad range of clinical manifestations as they occurred in a large family outbreak which apparently resulted from exposure to a single spore source. Presumably, differences in response of these individuals to their infection depended upon the intensity of exposure and factors of resistance. Although exposure has been shown to be an important determinant of severity of infection,[4] the relative importance of these two factors cannot be assessed in this outbreak.

Survey of the entire county in which the epidemic occurred has demonstrated an unexpectedly high over-all incidence of histoplasmin reactors. This is in contrast to predicted rates for Minnesota of 1 to 5 per cent.[33,91] Such a discrepancy may result from an irregular pattern of geographic concentration of high rates. If foci of high rates are present elsewhere in the state corresponding to those observed in Wright County, it might be expected that data on these areas of significantly high rates would be diluted out in sampling the entire state as has been done previously.

A concentration of reactors such as is present in the southeastern corner of Wright County prompts a search for locally operating factors, such as ground moisture, humidity, and proximity to bodies of water which might play a role in determining the prevalence and infectivity of the fungus. Although none of these factors seemed to be correlated with the prevalence of sensitivity, more detailed studies are required to determine their importance.

The results of this survey suggest that spread of histoplasmosis in this nonendemic area occurs from highly localized foci of *H. capsulatum* spores. In support of this contention is the occurrence of histoplasmosis as an epidemic involving a group of persons living on a farm surrounded by many farms on which no reactors live. This is further borne out in the Wright County survey data, in which a number of households were studied where skin sensitivity was found

TABLE 11
CLINICAL SPECTRUM OF HUMAN HISTOPLASMOSIS

Clinical type and severity	*Organs Involved*	*Age distribution*	*Frequency of occurrence*	*Prognosis*	*Laboratory findings*			*Remarks*
					Skin test	*Serology*	*Culture*	
CLINICALLY SYMPTOMATIC								
Disseminated[6, 8, 11, 40, 42, 43, 93]	R.E. system	Extremes of life	rare	poor	±	±	+	A few recoveries have been reported.
Acute pulmonary[2-5, 40, 42, 64, 93]	Lungs	All ages	uncommon	good	+	+	±	Clinical type often encountered in epidemics. May resemble atypical pneumonia. Often results in disseminated nodular pulmonary calcification.
Chronic pulmonary[66, 67]	Lungs	Older adults	undetermined	fair to poor	+	+	+	May resemble chronic progressive fibrocaseous pulmonary tuberculosis.
Chronic local[68]	Pharynx, larynx, etc.	Adults	probably rare	fair to poor	+	±	−	
CLINICALLY MILD OR ASYMPTOMATIC								
Pulmonary[2-5, 9, 40, 93, 98]	Lungs	All ages	common in endemic areas		+	+	−	May result in pulmonary calcification in 20-40% of cases.
Influenza-like illness[67, 93]	?	All ages			+	±	−	
No illness, no pulmonary calcification,[33]	?	All ages	very common in endemic areas		+	−	−	Asymptomatic acquisition of skin hypersensitivity in most persons may occur in this manner.

in several members of the family, in an area surrounded by farm families in whom no reactors were found. Demonstration of such a pattern does not support the hypothesis that spores are spread over a general area via air currents as has been suggested as the mode of spread of *Coccidioides immitis*. Rather, it supports previous evidence that *H. capsulatum* grows and is spread directly to humans from restricted areas in which environmental conditions are optimal. By this reasoning, the incidence of reactors in a given area would depend upon the number and accessibility of these sites of fungus growth, rather than upon air-borne spread enhancing factors in the environment. Investigation of the relationship between the geographic location of reactors and the presence of spores in their immediate environment would be particularly interesting in this area, and would perhaps add much to our knowledge of the ecology of this fungus.

The occurrence of an epidemic of clinical histoplasmosis, and the demonstration of an unexpectedly high local incidence of skin sensitivity to histoplasmin, in a county of southcentral Minnesota, should increase awareness among Minnesota physicians of the possible occurrence of this infection. On a basis of the data presented here, it might be predicted that sensitivity to the skin test antigen and cases of symptomatic pulmonary histoplasmosis in Minnesota might be expected to occur in family groups. It is also possible to predict that when suspicion of this fungus disease is raised in more and more patients with unexplained pneumonitis, the incidence of the disease in Minnesota will rise accordingly.

SUMMARY

The literature pertaining to histoplasmosis as a historic curiosity, as a clinical and laboratory entity, as a cause of nontuberculous pulmonary calcification, and as an epidemic pulmonary disease has been reviewed. An epidemic outbreak of histoplasmosis in a Wright County, Minnesota, farm family has been described, which involved at least 8 members whose illness ranged from a very mild pulmonary type to the fatal disseminated type of this disease. A source of infectious spores was shown probably to exist on the farm occupied by the involved family, although attempts thus far to isolate the fungus have failed. A survey to determine the prevalence of skin sensitivity to histoplasmin and tuberculin in Wright County revealed an unexpectedly high incidence of reactors to histoplasmin in the southeastern corner of the county. A higher incidence of sensitivity was shown to occur in rural dwellers than in urban dwellers. Data were presented to indicate that a higher incidence of reactors was found in some families than might be expected by chance alone. Chest x-ray survey of all reactors revealed an incidence of calicification of approximately 25 per cent, regardless of age. The implications and significance of these investigations are discussed, with presentation of a concept of the clinical spectrum of human histoplasmosis.

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The endobronchial instillation of oleaginous penicillin directly into the bronchus usually results in rapid disappearance of acute bronchopulmonary suppuration. In most cases, the patient's temperature returns nearly to normal the day after 2 or 3 cc. of a preparation representing 600,000 to 900,000 units of the antibiotic is introduced, reports A. Albert Carabelli, M.D., of St. Francis Hospital, Trenton, N. J., and the University of Pennsylvania, Philadelphia. Reversion of the sedimentation rate parallels clearing of the lesions, usually within one week, as demonstrated by roentgenograms. The method is recommended not only as prophylaxis against the development of chronic sequelae but also for poor-risk subjects before surgery.

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Management of Suppurative Bacterial Meningitis

ELLARD M. YOW, M.D.

Houston, Texas

As each new antibiotic is introduced, papers appear in the medical literature evaluating its effectiveness in the treatment of meningitis. Eventually an attempt is made to determine its relative place as compared to the previously accepted therapeutic agents. This final evaluation is quite difficult because of the problem of treating comparable groups of patients by the various means in statistically significant numbers. Factors other than the antimicrobial therapy also influence the outcome of the disease, particularly the extent of the damage to the central nervous system prior to the institution of therapy. Consequently, some differences of opinion arise not only as to the most effective drug for a particular form of meningitis, but also as to the best method of administering each antibiotic. These differences are not serious in most cases, since any of several antibiotics will usually eventually control the infection. The therapy of meningitis has progressed to the point today, however, that the objective of the physician is not only to reduce the mortality rate of meningitis, but to recognize and control the infection by the most rapid means available in order to prevent as much damage to the brain and its coverings as possible. The purpose of this paper is to suggest methods of controlling the common types of purulent meningeal infections (table 1).

Meningococcic meningitis usually develops as a result of the spread of meningococci to the meninges by way of the blood stream from a focus in the nasopharynx. If the diagnosis is to be made early, the stained sediment must be examined for organisms after centrifuging the spinal fluid. The usual routine laboratory can afford only a casual examination of this material, and the physician himself should carefully examine the slide.

Sulfonamide therapy is generally considered to be the basis for the treatment of meningococcic meningitis. An initial dose of 4 or 5 gm. should be administered intravenously, followed by an oral dose of 1 or 2 gm. every four hours. If parenteral administration of the drug must be continued, slightly smaller doses may be used. In our experience, sulfisoxazole has been as effective as sulfadiazine, if larger doses are administered, and it has the advantages of intramuscular administration as well as the freedom from renal complications. In severely ill patients, the rapidity of response may be increased by the simultaneous administration of aqueous forms of crystalline penicillin G given intramuscularly.

Pneumococcic meningitis is the second most common form of purulent meningitis in adults. Under best of circumstances, the disease is still quite serious with a mortality rate of from 15 to 30 per cent. The organisms may reach the meninges by direct extension via the lymphatics, bone, regional venous drainage from infections of the ear, mastoid, or paranasal sinuses, or it may be metastatic by way of the blood stream as a complication of a pneumonia or endocarditis. Penicillin is the drug of choice in pneumococcic meningitis. Dowling and associates[1] have reported that if doses in the range of 1,000,000 units of crystalline penicillin G are given every two hours intramuscularly, penicillin need not be administered intrathecally. Weinstein and associates,[2] on the other hand, reported better results using intrathecal doses of 30,000 units every twelve to twenty-four hours and smaller intramuscular doses. Most observers agree that a sulfonamide should also be given along with penicillin in pneumococcic meningitis in doses similar to those used in meningococcic meningitis.

The control of streptococcic pharyngitis and its complications has by administration of penicillin reduced the incidence of streptococcic meningitis to a relatively rare form. Prior to the use of the sulfonamides, this disease was always fatal, but today most cases can be promptly controlled by the parenteral administration of the rapidly absorbed forms of penicillin.

Meningitis due to Hemophilus influenzae re-

ELLARD M. YOW, *a 1943 graduate of Bowman Gray School of Medicine, is associate professor of medicine at Baylor University College of Medicine.*

TABLE 1

TREATMENT OF PURULENT FORMS OF MENINGITIS

Etiologic agent	*Antimicrobial agent*	*Route of administration*	*Daily dose*
Meningococcus	Sulfonamide	Parenterally initially	5 gm.
		Orally subsequently	6–12 gm.
	Penicillin G	Parenterally	100,000 U. q.4 h.
Pneumococcus	Penicillin G	Intramuscularly	1,000,000 q.2 h.
		Intramuscularly	100,000 q.3 h.
	or		
	and	Intrathecally	20,000 U.
	Sulfonamide	Parenterally initially	4–5 gm.
		Orally later	6–12 gm.
H. Influenzae	Streptomycin	Parenterally and	50–100 mg./Kg.
		Intrathecally	5–50 mg.
	Chloramphenicol	Orally or	100 mg./Kg.
		Parenterally	50 mg./Kg.
Staphylococcus	Penicillin or	Intrathecally	20,000 U.
	Bacitracin	Parenterally	500,000 U. q.3 h.
		Intrathecally	10,000 U.
		Intramuscularly	40,000–80,000 U.
	Tetracycline or	Orally	25 mg./Kg.
	Chloramphenicol	Intravenously	15 mg./Kg.
		Orally	100 mg./Kg.
		Parenterally	25 mg./Kg.
Streptococcus	Penicillin	Parenterally	500,000 U. q.3 h.
	If anaerobic streptococcus add 3.0 gm. to streptomycin daily.		
Coliform organisms	Streptomycin and	Parenterally	3–6 gm.
		Intrathecally	25–50 mg./Kg.
	Tetracycline or	Orally	2.0 gm.
		Intravenously	1–1.5 gm.
	Chloramphenicol	Orally	3.0 gm.
		Parenterally	1–1.5 gm.
Pseudomonas	Polymyxin B	Intramuscularly	2.5 mg./Kg.
	and	Intrathecally	2.5–5 mg.
	Tetracycline	Orally	2.0 gm.
		Intravenously	1–1.5 gm.
Proteus	Streptomycin	Parenterally	3–6 gm.
		Intrathecally	25–50 mg.
	and sulfona-	Parenterally	6–12 gm.
	mide or	Orally	6–12 gm.
	Neomycin	Intramuscularly	1–3 gm.
Friedlander's bacillus	Streptomycin and	Parenterally	3–6 gm.
		Intrathecally	25–50 mg.
	Chloramphenicol	Orally	3 gm.
		Parenterally	1.5 gm.
	or tetracycline	Orally	2 gm.
		Intravenously	1–1.5 gm.

mains one of the most common types of meningitis in young children, though it rarely occurs in adults. Chloramphenicol has recently been shown to be quite effective in the control of influenzal meningitis,[3] but others feel that the additional administration of streptomycin intramuscularly and intrathecally further reduces the mortality and the residual central nervous system damage.[2] The dose of chloramphenicol should be 100 mg. per kilogram per day in divided doses and 25 mg. of streptomycin may be dissolved in 10 cc. of sterile saline and injected slowly intrathecally.

Meningitis due to the staphylococcus most often occurs as a complication of a bacteremia, but may develop as a result of extension from the mastoids, middle ear, or paranasal sinuses, or as a contaminant of surgery or trauma to the central nervous system. Penicillin is the drug of choice in infections due to sensitive strains. It should be administered in large parenteral doses, 500,000 units or more every three hours, and 20,000 units intrathecally daily. Many strains are resistant to penicillin, however, and other antibiotics should be resorted to, such as bacitracin, chloramphenicol, tetracycline, or streptomycin. Because of the seriousness of the disease, use of some other antibiotic with penicillin is generally wise until the results of the sensitivity tests are known. Erythromycin is quite active against most strains of staphylococci, but there is little clinical or experimental evidence to show that it appears in the spinal fluid in adequate concentration. Consequently, it should not be used alone in the treatment of staphylococcic meningitis.

The gram-negative bacilli are more frequently encountered as the causative organisms in purulent forms of meningitis than previously and are usually the complication of a blood stream infection. But, meningitis may complicate traumatic injuries or surgical procedures involving the central nervous system. Proteus and Pseudomonas may occasionally spread from an infected middle ear or mastoid. The drug that will be most effective in the treatment of meningitis due to coliform organisms is difficult to predict

because of the wide variation of antibiotic sensitivity. Consequently, in vitro testing of the individual strains involved becomes extremely important. Streptomycin should be administered both intramuscularly and intrathecally in infections due to sensitive strains. Some antibacterial agent should be given with streptomycin because of the possibility of initial or developed resistance. Administration of one of the tetracycline analogues or chloramphenicol is usually wise until the sensitivity of the causative organism is known. Polymyxin B is most consistently effective in the management of infections due to Pseudomonas aeruginosa and is also active against most other gram-negative bacilli except Proteus. It should be given in intramuscular doses of 2.5 mg. per kilogram per day and intrathecally in a total dose of 2.5 to 5 mg. daily. Bunn[4] has reported that Terramycin and polymyxin act synergistically against Pseudomonas. He has observed excellent results in some infections by giving 1 injection of 25 mg. of polymyxin B daily with 2 gm. of Terramycin daily by mouth. Neomycin is most consistently effective against the Proteus group of organisms. The recommended intramuscular dose in acute infections is 10 to 15 mg. per kilogram per day.

In spite of very diligent attempts to establish an etiologic diagnosis, previous therapy sometimes makes this impossible. Attempts must then be made to determine clinically the most likely causative organism and to direct therapy toward the suppression of that organism. However, if specific diagnosis is not made, the therapeutic regime must be planned to cover other likely etiologic possibilities in order to avoid loss of time in controlling the infection.

Many of the complications and sequelae of meningitis, such as hydrocephalus, subdural empyema, cranial nerve palsy, epilepsy, and cerebral deterioration seen prior to the use of effective antimicrobial agents are relatively rare today. Attention has been called to other complications which are apparently the result of the ability of the antibiotics to suppress the causative organisms without reversing the pathologic changes. A very common complication of meningitis of all types in infants is the production of serous subdural effusions.[5] These are also occasionally seen in older children and adults, particularly after pneumococcic meningitis, and should be suspected in any patient who does not respond as promptly as should be expected, or if signs of increased intracranial pressure recur after initial improvement.

Although the infection is controlled, patients with meningitis still develop cerebrovascular thrombosis, adhesive arachnoiditis, degenerative changes of the nerves or roots, and cortical and subependymal changes as a result of meningitis. We have observed clinical findings in patients with pneumococcic meningitis which suggested localization of the infection process, who at operation or autopsy were found to have a localized or diffuse inflammatory reaction of the cerebrum without suppuration referred to by the pathologists as "cerebritis."

Studies of Weinstein and associates[2] reported a decreased incidence of complications after meningitis by supplementing systemic antimicrobial therapy by carefully administered intrathecal injection of antibiotics. They also found that the spinal fluid became sterilized more rapidly when the intrathecal route was used. It seems reasonable to expect that the more rapidly the infectious process is controlled, the less the extent of damage is to the central nervous system and the fewer the residual complications.

In our own experience, we have seen examples of meningitis due to staphylococci and Pseudomonas which resulted from the introduction of organisms into the subarachnoid space associated with neurosurgical procedures or the administration of spinal anesthesia, in which the spinal fluid could not be sterilized in spite of intensive systemic therapy until the effective antibiotics were injected intrathecally.

The intrathecal administration of antibiotics has been abandoned in some clinics on the grounds that it is dangerous. This is based on the experimental study of the direct application of solutions of antibiotics to the cerebral cortex and the residual brain damage seen in some patients with meningitis who have received antibiotics intrathecally. There is no direct evidence, however, of damage in man unless the dose of penicillin is 50,000 units or greater. Late effects of intrathecal antibiotics in meningitis are quite difficult to evaluate, since the disease process itself may produce all of the changes described. As a matter of fact, there is evidence that incidence of these changes may even be decreased by the intraspinal administration of antibiotics.[2]

Certain precautions should be taken when administering antibiotics by the intrathecal route. The most important of these is to stay within the recommended doses. The quantity of penicillin should not exceed 30,000 units and streptomycin should be 50 mg. or less. The maximum intrathecal dose of polymyxin B is 5 mg. and of bacitracin, 10,000 units. It is important that the antibiotic be dissolved in 10 cc. of physiologic saline and injected over a period of approximately ten minutes. If the antibiotic is injected into the

ventricles or cisterna magna, the dose should be smaller than that introduced in the lumbar area, in the range of one-third to one-half the dose.

Generally speaking the only antibiotics that should be injected intrathecally are penicillin, streptomycin, bacitracin, and polymyxin. The others are not only too irritating, but with the exception of Erythromycin, adequate spinal fluid concentrations are achieved by systemic administration.

SUMMARY

It should be emphasized that the primary objective of the therapy of meningitis is the rapid control of the infection by achieving therapeutic serum and spinal fluid levels of the appropriate antimicrobial agent. Whether or not the intraspinal injection is necessary depends on several factors, such as the type of antibiotic being used, the blood levels achieved, the rate of diffusion across the meninges, the sensitivity of the etiologic organism to the antibiotic being administered, the age of the patient, and the mode of entrance of the invading organism. If massive doses of penicillin are used, intrathecal injection of penicillin may not be necessary in the treatment of pneumococcic meningitis. On the other hand, if small systemic doses are used, intrathecal injection may be necessary. If the etiologic organism is extremly sensitive to the antimicrobial agent being administered systemically, as in the case of the sulfonamides and meningococci, or penicillin and hemolytic streptococci, intrathecal administration is usually not indicated. Gram-negative bacilli are relatively resistant to most antibiotics, so that, if there is an antibiotic that can be administered intrathecally which is active against the particular organism, higher local concentration can be attained.

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The antibiotic preparation Biomydrin Otic has proved effective treatment for otitis media and externa. Successful treatment of 88.7 per cent of 282 patients with acute or chronic infections is attributed by A. M. Lazar, M.D., and Milton Goldin, M.S., of Chicago Medical School and Mount Sinai Hospital, Chicago, to this combination of neomycin sulfate, gramicidin, thonzylamine hydrochloride, and Thonzonium bromide in an aqueous vehicle of properly acidic reaction. Usually 4 drops of the medicament are instilled into the affected ear three times a day and medication is continued for two or three days after apparent recovery. Circumscribed otitis is most frequently caused by staphylococci and other gram-positive organisms, and the diffuse form by gram-negative *Pseudomonas aeruginosa* and strains of *Proteus*.

A. M. Lazar, and Milton Goldin: Eye, Ear, Nose & Throat Monthly 33:351-359, 1954.

A Clinical Comparison of Bulk and Stimulant Laxatives

LEO J. CASS, M.D., AND WILLEM S. FREDERIK, M.D.

Boston, Massachusetts

For one hundred years milk of magnesia has been used as a laxative, yet a search of the literature reveals essentially no record of a quantitative or controlled study of its effectiveness, although many references are made in the therapeutic field to its use. The medical value of this substance is taken for granted.

For a proper understanding of the patterns and properties of various laxatives in relation to one another, they must be studied side by side in the same patient. In such experiments, however valid, quantitative comparative data can be obtained only when the preparations are studied under truly blind conditions, where neither patient nor observer knows the nature of the medications. The following quantitative study was undertaken to compare milk of magnesia and methylcellulose as laxatives. Many studies are available on methylcellulose as opposed to more irritating substances, but, in this study, we are interested in a comparison of a substance more similar to methylcellulose.

The technic of obtaining quantitative clinical data in regard to the use of laxatives has been outlined in a previous publication; however, the fundamental principles of such a study bear repeating. They are: randomized sequence of administration and double-blind conditions. The preparation of tablets, method of coding, and choice of placebo or control should be carried out in such a fashion as to insure, so far as possible, that neither observer nor subject can identify the medication. Using this technic, subjective observations can be converted into a quantitative impartial basis for comparing medication. By assigning numerical values to the various degrees of subjective change, the data may be subjected to statistical analysis with relative ease and in this fashion quantitative comparisons carried out.

The optimum type and number of movements per day for most people consist of one soft movement. Obviously, the number of bowel movements alone is not a complete criterion. The ideal number varies with dietary habits, age, activity, acquired intestinal patterns, and personal characteristics. The consistency of the stool, the well-being of the individual, and the personal satisfaction all contribute to the criteria of effectiveness. These factors may vary in importance with the age of the patient and the degree of constipation, and laxatives vary in their ability to affect these criteria. We have previously reported upon the relative effects of bulk laxatives, pointing out their advantages and disadvantages.[1] We have also studied the effects of certain laxatives on stool consistency and frequency.[2] It becomes obvious that modification of the stool content alone is sometimes insufficient. This study was undertaken to clarify the importance of each of these two aspects—number and consistency—in regard to methylcellulose and milk of magnesia.

METHODS

Studies were carried out in the Chronic Disease Hospital, Long Island, Massachusetts, on 1,200 patients. The 45 subjects in this study were all semiambulatory (bed or chair), permanently institutionalized, and severely constipated individuals. The medications were administered by a technician, and observations were made by a full-time nurse who did not know the code. All persons received the medication at the same time each day. The medication period was ten days, at the end of which time the patients were abruptly shifted to the next medication. The order in which medications were given varied in a random fashion. All medications were identical in appearance, taste, and color. The active ingredients of the medications were as follows: (1) methylcellulose tablets—methylcellulose (BL grade) 0.500 gm.; (2) milk of magnesia tablets—

LEO J. CASS, *a 1938 graduate of Harvard Medical School, is assistant medical advisor in the Harvard department of hygiene and visiting physician at Long Island Hospital, Boston.* WILLEM S. FREDERIK, *a 1940 graduate of the University of Utrecht, Holland, is research associate in the department of physiology, Harvard School of Public Health.*

magnesium hydroxide powder at 73 per cent 0.444 gm.; (3) laxative tablet (placebo)—milk sugar 0.400 gm.

All the tablets were the same size and were similarly colored and flavored. They also were given a light coat of shellac with a small amount of charcoal to further mask any differences between them. This put the milk of magnesia tablets in a relatively disadvantageous position, since it is possible to give the present dose in a smaller tablet than had to be used here to maintain the blind-test conditions.

The medication was administered twice a day, 4 tablets in the morning and 4 at night, or a total of 8 tablets per day. The obvious prejudice against taking so many pills was recognized, but due to the necessity for achieving blind conditions, no other course was possible, since the dose of methylcellulose requires a minimum of at least 6 tablets a day. To be sure that adequate amounts of methylcellulose were being given, it was decided to use 8 tablets.

The patients were questioned as to: (1) number of stools each day; (2) consistency of stools, whether watery, soft, or hard; and (3) side effects such as nausea, vomiting, cramps, distention, and tenesmus.

Observations were carried out at the same time each day. No other laxatives were given during the entire study. If a patient failed to have a bowel movement for three days, an afternoon enema was administered and the medication carried on. No patient had to discontinue medication because of an excessive number of movements. There were 44 patients who completed the entire series of ten days for each medication and all were observed on schedule.

DISCUSSION OF RESULTS

Frequency of bowel movements. The frequency of bowel movements during the period of treatment shows a significantly higher number for milk of magnesia and methylcellulose treatment than for lactose (placebo) administration.

Table 1 shows the type of medication administered, the number of patients observed during ten days, the average number of bowel movements per period of ten days, and the standard deviation.

As follows from table 1, milk of magnesia gives

TABLE 1

Treatment	*Number of patients*	*Bowel movements for 10 days* Average	Standard deviation
Lactose	44	5.614	3.507
Methylcellulose	45	8.044	2.565
Milk of magnesia	44	9.022	2.518

TABLE 2
MILK OF MAGNESIA VERSUS METHYLCELLULOSE

Source of variation	*Degrees of freedom*	*Sum of squares*	*Mean square*	
Total	87	593.989		
Between patients	43	375.489	8.732	
Between drugs	1	23.011	23.011	
Residual	43	195.489	4.546	
	F—Values		P=5%	P=1%
	Patients/residual	1.92	1.67	2.07
	Drugs/residual	5.06	4.06	7.25

a slightly higher bowel movement frequency than methylcellulose. The critical ratio between methylcellulose and the placebo is 3.7; between milk of magnesia and the placebo, 5.2; and between milk of magnesia and methylcellulose, 1.8. Therefore, we may conclude that methylcellulose, as well as milk of magnesia, definitely increases the frequency of bowel movements. The critical ratio between milk of magnesia and methylcellulose is just short of the 5 per cent level of significance.

A more sensitive statistical analysis of the data, however, justifies the conclusion that milk of magnesia provides a significantly higher frequency of bowel movements than methylcellulose (table 2). Because of the design of this kind of experiment, approximately two-thirds of the patients receiving a placebo, received in the previous period either methylcellulose or milk of magnesia. By the same token, approximately one-third of the patients receiving milk of magnesia or methylcellulose, received in the previous treatment period a placebo, lactose. Therefore, during the first couple of days of the new treatment, a persisting influence of the previous medication can be expected. The results with the placebo will, therefore, be influenced favorably in the first few days in two-thirds of the patients who previously had received a laxative, because of the persistence of the response.

For this reason, an analysis was made of the trend of the bowel movement frequency during the ten-day period of treatment.

Table 3 lists for each drug the average number of bowel movements on each day of treatment.

Graph 1 presents these data in graphic form (dotted lines).

For the sake of simplicity, a straight-line trend during this period of test is assumed. The equation for a straight line is $y = a + bx$. The number of observations of patients, and probably the duration of the test periods, are too small to justify further mathematical treatment.

From graph 1, the impression is obtained that a major change in bowel frequency takes place

TABLE 3

Treatment	*Average number of bowel movements on each treatment day*										*Over-all day average*
	1	2	3	4	5	6	7	8	9	10	
Lactose	.80	.71	.59	.55	.57	.43	.59	.48	.43	.48	.561
Methylcellulose	.99	.71	.78	.91	.78	.91	.84	.71	.82	.89	.804
Milk of magnesia	.73	.91	.86	.91	1.00	1.00	.86	.84	1.00	.91	.900

during the first four or five days of treatment. Therefore, curve-fitting is also done for the first five days, as well as for the last five days of each treatment (solid lines).

The "b" is negative during the first five days of lactose treatment and positive during this period for methylcellulose and milk of magnesia. A negative "b" means a declining trend of the straight line, indicating a decrease of the number of bowel movements during the period of observation. A positive "b" indicates the opposite.

Milk of magnesia shows the fastest increase in bowel movement frequency during the first five days of treatment.

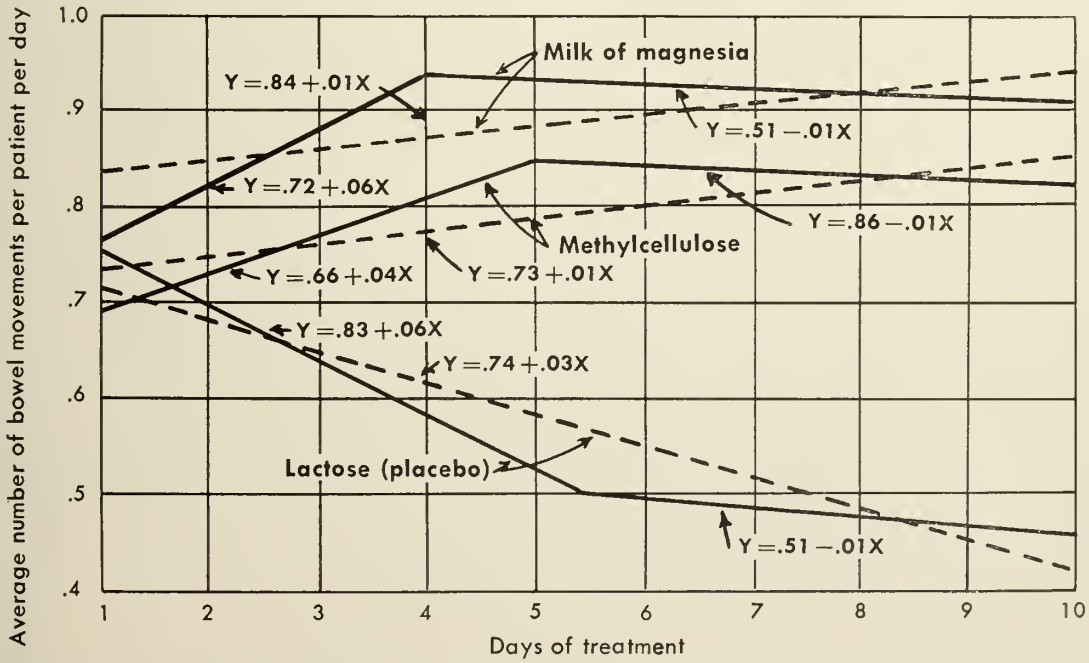
The last five days of treatment show a slight but not significant decrease in bowel movement frequency for all 3 drugs.

Consistency of bowel movements. Every bowel movement was judged by the observer as to its consistency, 1 = watery; 2 = normal/soft; 3 = hard. By doing so, the data can be subjected to statistical treatment.

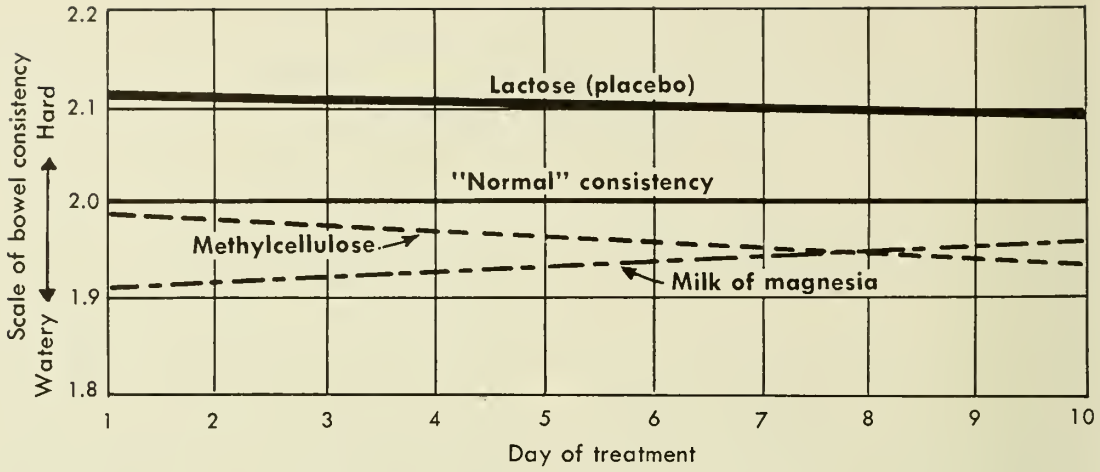
The consistency of the stools, as a result of the treatment with methylcellulose and milk of magnesia, shows a significantly lower figure than the consistency after the placebo, lactose. The critical ratio between placebo and methylcellulose is 4.36; between placebo and milk of magnesia, 5.34; and between methylcellulose and milk of magnesia, .98. It follows, therefore, that milk of magnesia, as well as methylcellulose, definitely softens the consistency of the stools. It is impossible to prove a significant difference in fecal consistency between milk of magnesia and methylcellulose. Graph 2 shows the average consistency per day of each of the treatments. The consistency due to the placebo is well above the consistency resulting from the 2 laxatives. The downward trend of the placebo curve is due primarily to a few patients in whom we were forced to use an enema (table 4).

TABLE 4

	Total number enemas	*Tenesmus and cramps*	*Fullness*	*Gas*
Lactose	19	5	11	1
Methylcellulose	1	0	0	0
Milk of magnesia	2	0	0	0



Graph I. Presentation of average daily bowel movement per drug. Curves are fitted to the 10 daily averages (dotted lines) and to the first and last 5 daily averages (solid lines).



Graph 2. Presentation of average daily stool consistency per drug. Lines are fitted to the 10 daily averages, using the method of the "least squares" and assuming a straight-line trend.

Side effects consisted of tenesmus, cramps, and a sense of fullness and were frequently present in the placebo series. The use of either methylcellulose or milk of magnesia abolished these side effects completely.

CONCLUSIONS

Methylcellulose and milk of magnesia are both effective laxatives, producing approximately the same cathartic effects when given under strict supervision. The use of these laxatives abolished the gas, tenesmus, and fullness which were common symptoms when no laxative was given. The large number of tablets required to maintain an adequate dose of methylcellulose was a disadvantage as compared to milk of magnesia.

The inadequate number of bowel movements and the accompanying side effects in the period of placebo medication negates the frequent supposition that laxatives are unnecessary in such a population of chronically constipated patients.

Studies were carried out under a grant from Sterling-Winthrop Research Institute. We wish to thank the Charles H. Phillips Co. for the supply of milk of magnesia for this study.

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If antibiotics are given prophylactically for long periods, infections complicating diabetes mellitus occur less frequently. Among 94 diabetic patients receiving 500 mg. of Aureomycin daily for more than nineteen months, Leon V. McVay, Jr., M.D., and associates of the University of Tennessee and the John Gaston Hospital, Memphis, find that the incidence of urinary and respiratory ailments declined, the general health improved, and the patients felt better. Toxic reactions to the drug were slight. Concomitant administration of Paraben, the methyl and propyl esters of parahydroxybenzoic acid, prevented the overgrowth of the fungus *Candida albicans.*

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Psychiatric Use of Dehydroisoandrosterone in College Students—A Pilot Study

H. DOUGLAS LAMB, M.D.

Minneapolis, Minnesota

In 1952, workers at St. Bartholomew's Hospital, London[1] and a special juvenile unit at St. Ebba's Hospital, Epsom, England[2] described 2 experiments on the treatment of adult schizophrenics and inadequate personality in juveniles, respectively, with dehydroisoandrosterone, the "beta fraction" of the adrenocortical steroids. These authors' conclusions were cautious and they stressed the fact that the administration of dehydroisoandrosterone would probably have to be continued for a longer period than the few months they allowed for lasting results to be obtained. The improvement in the schizophrenic group was not conspicuous. The juvenile group whose average age was 15 did much better, and it was noted that those who responded to treatment showed "a pattern of physical immaturity (even effeminacy), timidity, social inadequacy, and lack of drive." A noteworthy feature of the results—apart from a pronounced increase in self-confidence and aggressiveness—was the alteration of homosexual to heterosexual tendencies. No correlation was found between the patients' urinary excretion of 17 ketosteroids and their response to treatment.

To the psychiatrist attached to a student health service in a large university, students with inadequate personalities present a treatment problem out of all proportion to their numbers on the campus, which fortunately are small. They are without a goal, pathetic, frightened creatures who make poor grades, and take little or no part in the ordinary social life of their fellows. They sometimes drift passively into crude homosexual relationships through their fearfulness and lack of initiative which precludes their trying to date the homeliest girl. It is only too obvious that many of them will gain little or nothing from their stay at college, to which they have come only as a result of social pressures and "conformity." Though it is nowadays recognized that the long-term prognosis is not as hopeless as it was thought only a few years ago, since we know how many persons mature late and how surprisingly well some inadequate people do under the thumb of a suitable spouse, nevertheless, the impression remains that a large proportion of them will probably remain the white-collar equivalents of "hewers of wood and drawers of water," providing psychosis does not first overtake them. Any method of treatment which offers a chance of improving the self-confidence and initiative of such patients merits a trial, since they do not respond to individual psychotherapy in any degree proportionate to the amount of time which must be expended upon them, and for various reasons group psychotherapy is often impracticable, at any rate in a voluntary setting.

It was decided to start a pilot study with buccal administration of 25 mg. doses of dehydroisoandrosterone to 11 patients selected on clinical grounds only. In order to obviate as far as possible the element of suggestion, the patients were not told about the nature of the drug other than that it might be of benefit and would not be harmful. If a patient asked "What changes am I to expect?", he was told that he must observe changes for himself, if and when they should occur. Moreover, none of the patients received psychotherapy during the administration of dehydroisoandrosterone. All were seen regularly at weekly interviews, which were kept as short and brusque as possible so as to reduce the supportive situation to a minimum. Also, as it happened, none of the patients in this preliminary study knew any organic chemistry. It would, of course, be naive to expect that with these precautions some element of benefit from suggestion, therapeutic relationship, and feeling that some definite active steps were being taken on their behalf can be excluded, and the number of patients available for the pilot study was too small for a control group who would receive treatment only with placebos. Nonetheless, the patients selected were very unpromising material

H. DOUGLAS LAMB, *a 1937 graduate of Guy's Hospital Medical School, London, is assistant professor of neurology and psychiatry and mental hygienist to Students' Health Service, University of Minnesota.*

for psychotherapy even of a crude sort, and it would seem reasonable to suppose that nonphysiologic factors in any improvement which took place were very small.

METHOD OF ADMINISTRATION

The patients were provided with a week's supply of dehydroisoandrosterone, which was renewed at each weekly checkup. The dosage varied from patient to patient, an average being 25 mg. on alternate days. Urinary ketosteroids were not estimated (v. supra.). When, in the opinion of the therapist, the course was completed, the patient was asked to write a brief description, covering one side of a page at most, on any changes which he felt had taken place in himself since taking the medication. The course was considered completed when the patient had made no significant further improvement four weeks, that is, twelve treatment days, after attaining a reasonably satisfactory adjustment.

TYPICAL EXAMPLES

Case 1. Harry S., age 20, complained of shyness, daydreaming, inability to make friends, "fuzziness" in thinking, and persistent feelings of inferiority. After 39 doses of 25 mg. of the drug, he wrote: "Once again I am able to think clearly and precisely. I no longer find myself frequently upset or in a state of stupor. Problems that before seemed great are no longer bothersome and those things that do come up are coped with quickly and without much trouble. . . . I find that my sociability has increased. When with others I now have a sense of being at ease, whereas before among people I was on edge and hardly dared to speak." This was written six weeks after last dose.

Case 2. Ken B., age 19, complained of intense shyness, particularly with the opposite sex, lack of concentration and initiative. This boy was wholly dominated by a very aggressive buddy who even chose his girl friend for him. After 55 doses of 25 mg. of dehydroisoandrosterone, he wrote the following four weeks after the last dose: "I find myself talking to people much more than before. I had usually let other people speak to me first and carry on most of the conversation. It wasn't that I didn't want to talk to them, I just felt I never had anything worth saying. Now I not only do my share of talking but sometimes force the conversation, even though I feel I bore the listener. There were days when I became very depressed and irritable. After taking the medication, the mood wore off in a few hours even though nothing had changed in my environment. I feel more 'solid,' that is, I feel more that I'm an individual with opinions of my own. I had always taken what was given to me without any spoken complaints or question. Now I'll spout my opinions even though I'm tactless." This boy later became engaged to a girl of his own choosing, and, when last heard from six months later, was undergoing training for a jet pilot!

Case 3. Larry K., age 18, complained of persistent feelings of inferiority with frequent brief bouts of depression lasting from an hour or two to a few days, which always developed when he received some minor disappointment such as a poor grade in a test. After 40 doses of 25 mg. of dehydroisoandrosterone, he wrote, "I continue to have my periods of depression, but they gradually become fewer and of much shorter duration. The feeling of inferiority is lessened and I feel much more able to tackle problems which arise. Although I'm still not a very good student, I don't feel a sense of defeat when I do have difficulties." He wrote, six months later, "I've been getting along pretty well and have nothing to complain about. Of course, I haven't had any hard studies since last fall but feel confident that I can handle the course in electronics which is starting soon. (Patient was now in the Navy.) "In general I haven't had the nervousness and lack of confidence that I had last year."

From the total of 11 subjects treated, 4 others made similar definite improvement which was maintained six months after the last dosage. Improvement occurred in 1, but he is still under treatment with dehydroisoandrosterone, and 3 are regarded as failures. Of these 3 failures, 2 were simple schizophrenics, 1 of whom gave up treatment after eight days, and the other showed no sign whatever of improvement after 85 doses of 25 mg. The third was a bisexual who, during treatment, began to show increased desire for overt homosexual experiences and as he put it, "a desire to let my hair down generally," so that treatment was stopped immediately.

SUMMARY

In a small pilot study of 11 students selected because of predominant complaints of inadequacy and treated with varying dosages of dehydroisoandrosterone without concomitant psychotherapy, 8 showed definite improvement in initiative, self-confidence, and level of academic work, together with better socializing capacity and a more realistic and aggressive attitude in general. A bisexual student became more uninhibited and more overtly homosexual during treatment, and 2 cases, both simple schizophrenics, showed no improvement. It is again emphasized that the number of cases is too small to warrant definite conclusions, but, nonetheless, the results are considered encouraging enough to merit further study with a larger group and with adequate controls.

Thanks are due to Organon, Inc., Orange, New Jersey, for providing a supply of dehydroisoandrosterone for investigational use and to Dr. Elizabeth Frame, lately of the biochemistry department, University of Minnesota hospitals, for her interest and technical advice.

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Roentgenographic Examinations of the Lower Back on Applicants for Employment

ROLF M. IVERSON, M.D.
Minneapolis, Minnesota

THE ROUTINE pre-employment roentgenographic examination of the lumbosacral spine in itself is simple enough. To obtain the fullest benefits from it for the employer and the employee presents a number of problems, and these may very well increase as its use becomes more general. It is relatively easy for the radiologist to report the findings, but in an examination where relatively normal or symptomless backs reveal perhaps 50 per cent anomalies and other bony variants, the evaluation of these findings becomes a rather complicated problem. The use of the roentgenographic examination does not preclude a thorough clinical examination and evaluation. The majority of the roentgenographic findings are minor. Findings which were in the past considered significant have more recently been considered relatively insignificant. Now these same findings must be re-evaluated from the standpoint of the industrial back. For the present we must utilize our own past experiences and those of others which are recorded in the literature to evaluate roentgenographic findings.

LITERATURE

In 1929, Bohart[1] reported on roentgenographic examinations of 1,000 symptomless spines. Anomalies and anatomic variations from normal were revealed in 40 per cent. The anomalies were most common at the lumbosacral joint. The men with the anomalies were employed. He estimated that, of those who had anomalies, 40 to 50 per cent experienced trauma after employment. He was of the opinion that the anomalies did not participate in the injuries or delay recovery from the injury. However, he felt that hypertrophic changes seem almost certain to produce back complaints.

Cushway and Maier[2] reported in 1929 on the roentgenographic findings in the spines of 931 patients who had passed a rigid physical examination in application for work as switchmen and firemen on the Belt Railroad in Chicago. Out of the 931 patients, 414 had a total of 510 anomalies and abnormalities.

Breck and associates[3] reported in 1944 on the roentgenographic findings in the lumbar spines of 450 consecutive applicants for heavy work. Several large adverse legal judgments led to this procedure as the authors felt the allegedly injured individuals with low back complaints had pathology which undoubtedly existed prior to the injury. They felt the most serious findings were hypertrophic changes, old compression fractures, spondylolisthesis, sacro-iliac arthritis, transitional vertebrae, and structural scoliosis. Of those examined, 31 per cent showed significant pathologic changes. Only 15 per cent were rejected for work.

Barton and Biram[4] reported in 1946 on 1,000 consecutive x-ray examinations of the lumbar spine. Of these, 502 patients were considered normal; 498 revealed a total of 856 defects and anomalies. Three groups of patients were compared: (1) 100 preselected cases, all with signs or history of back trouble; (2) 100 consecutive cases, 36 with signs or history of back trouble; and (3) 100 preselected cases without signs or history of back trouble. The group with signs or symptoms of back trouble showed a larger incidence of arthritic changes, scoliosis, spondylolisthesis, spina bifida occulta of the fifth lumbar vertebra, and evidence of trauma or fracture.

Allen and Lindem[5] reported in 1950 on 3,000 x-ray studies of the lumbosacral spines in applicants for work in an industrial plant between June 1, 1948 and June 1, 1950. The ages of the applicants ranged from 18 to 65 years.

Osteoarthritis was found in 408 or 13.6 per cent; 34 or 1.13 per cent revealed evidence of degenerated intervertebral disks; 89 or 2.96 per

ROLF M. IVERSON, *a 1939 graduate of Northwestern University Medical School, is a specialist in roentgenology and radiology.*

*Presented before the Great Northern Railway Surgeons Association at Great Falls, Montana, on June 28, 1954.

cent showed old fractures; and 491 or 15.45 per cent revealed congenital or developmental lesions.

It is interesting that they noted a pronounced decrease in prolonged disabling lower back conditions and subjective back complaints when they were able to show the patient conditions in his back which existed at the time of employment.

We have reviewed the first 81 pre-employment roentgenograms of the lumbosacral spine done for the Great Northern Railway in this office (table 1). The roentgenograms were made as follows:

1. Single 14- by 17-inch anteroposterior view of the lumbar spine including the eleventh dorsal vertebra and the sacrum.
2. Single 14- by 17-inch lateral view of the lumbar spine including the eleventh dorsal vertebra and the sacrum.
3. Single 10- by 12-inch lateral view centering at the lumbosacral joint.

TABLE 1
ANALYSIS OF LUMBOSACRAL ROENTGENOGRAMS FOR GREAT NORTHERN PRE-EMPLOYMENT EXAMINATIONS

	No. of cases	*Per cent*
Total number of cases	81	
Normal	34	43
Abnormal	47	57
Total abnormalities	74	
Spina bifida occulta	18	
Scoliosis, minimum	12	
Asymmetrical facets	11	
Hypertrophic changes, minimum	6	
Transitional vertebrae	5	
Bilateral: 3		
Unilateral: 2		
Spondylolisthesis	3	
Spondylolysis	1	
Fractures, minimum	4	
Old epiphysitis	4	
Ununited epiphyses	3	
Slight narrowing, lumbosacral joint	3	
Schmorl bodies	3	
Opaque media, spinal canal	1	

DISCUSSION

The minor roentgenographic anomalies must be evaluated according to the patient's physical condition, muscular development, posture, and so forth. A well-developed musculature certainly can compensate to a considerable degree for bony variants.

Scoliosis of a minimal degree occurs quite frequently and probably is not significant. More pronounced degrees of scoliosis, whether postural or structural in nature, lead to premature development of degenerative disk changes and hypertrophic lipping.

Schmorl bodies are found often and are not regarded as significant unless associated with narrowing of the intervertebral disk space.

The size and symmetry of the facets at the lumbosacral joint are regarded by some men as significant in regard to the stability of the lumbosacral joint. Abnormally small facets and pronounced asymmetry of the facets may be important. A review of our cases revealed: (1) vertical facets—15 per cent, (2) asymmetrical facets —15 per cent, and (3) AP facets—70 per cent. In this particular group, the facets all appeared to be average in size.

Probably the lumbosacral angle is more important. The hyperlordotic lumbar spine with the horizontal sacrum and the resultant steep lumbosacral angle would seem to be susceptible to back strain, and, because of this, is a poor industrial back. According to Ferguson,[6] the stable lumbosacral angle is one in which the inclination of the superior surface of the sacrum to the horizontal is not over 42 degrees. The lumbosacral "pitch" can be judged quite well on the routine lateral film. If the lumbosacral angle is over 45 degrees or if a vertical line drawn through the center of the third lumbar vertebra projects an inch or more anterior to the upper anterior margin of the sacrum, it is significant. In this short series of cases, the lumbosacral angle was not judged to be abnormally steep in any individual.

Spina bifida occulta of the upper sacrum occurs too frequently to be regarded as significant. Spina bifida occulta of the fifth lumbar vertebra should be regarded as more significant because this defect is more often observed in cases of spondylolysis and spondylolisthesis at the lumbosacral joint.

Transitional vertebrae are generally regarded as significant. Complete bilateral sacralization is of questionable significance. Bilateral sacralization with false joints and unilateral sacralization or lumbarization are generally regarded as productive of low-back complaints.

Narrowed interspaces are of definite significance, particularly in the younger individuals. However, men vary considerably in their evaluation of a slight degree of narrowing of the interspaces, particularly at the lumbosacral joint. I would question the significance of a slight degree of narrowing of the lumbosacral joint space unless there are associated hypertrophic changes. The narrowing of the lumbosacral interspace associated with transitional vertebrae is, I believe, developmental and not degenerative in origin.

Spondylolisthesis and spondylolysis are defi-

nitely significant and a liability to the employer and the employee. Unilateral spondylolysis is also significant. In routine anteroposterior and lateral views, cases of spondylolysis are going to be missed. For that reason, I consider a spina bifida occulta of the last lumbar vertebra significant and believe oblique views are indicated for further study to prove that spondylolysis is not present.

Old minimal fractures are significant primarily because they should be recorded in the patient's history. Moderate degree fractures of the vertebral bodies are significant and more so if associated with localized hypertrophic changes and narrowing of the disk spaces.

Sacro-iliac arthritis is of grave significance in young individuals, particularly as this usually indicates a progressive rheumatoid arthritis. Hypertrophic arthritis in the sacro-iliac joints is rare in young individuals.

A residuum of opaque media in the spinal canal would, I believe, automatically disqualify an individual.

Hypertrophic changes seem to be regarded as of considerable significance by the men who have made studies in this field. Minimal changes are, I believe, important particularly in the younger age group. If individuals over the age of 40 are being employed, this finding must be anticipated. When the changes are more pronounced in degree, localized changes with associated narrowing of disk space are especially significant.

Minor degrees of epiphysitis are probably not significant. Residual evidence of a more generalized epiphysitis is more significant, particularly when associated with anterior narrowing of the vertebrae as these cases are more prone to develop hypertrophic arthritis.

CONCLUSIONS

Pre-employment roentgenographic examinations of the lumbosacral spine, the part of the employee's low back which is subject to trauma, are invaluable to the employer and to the physician. These examinations will not eliminate back complaints. They will aid in eliminating potentially weak backs. More important, they provide a record of the applicant's lumbosacral spine for future reference and for comparative purposes in evaluating future trauma and low-back complaints.

In the pre-employment roentgenographic examination of the spine, the following findings are significant: (1) spondylolisthesis or spondylolysis, (2) localized hypertrophic changes particularly when associated with narrowing of the disk space, (3) hypertrophic changes in the younger age group, (4) definite narrowing of a disk space, (5) unilateral sacralization or lumbarization of a vertebra, (6) bilateral sacralization with false joints, (7) fractures of the vertebral bodies, (8) steep lumbosacral angle, and (9) structural scoliosis or moderate postural scoliosis.

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Motor and sensory paraplegia may be induced by translumbar aortography. Areas below the eighth thoracic cord segment were completely paralyzed in a patient examined with 70 per cent sodium acetrizoate (Urokon) to demonstrate a possible aortic aneurysm. Recovery was spontaneous but partial. Substitution of Urokon, iodopyracet (Diodrast), and sodium iodomethamate (Neo-Iopax) for sodium iodide has eliminated all but transient side-effects with aortographic examination, but Saul Boyarsky, M.D., of Duke University, Durham, N. C., emphasizes that injection should not be made below the twelfth thoracic vertebra. Importance of the information to be gained should be weighed against the possible risk involved.

Saul Boyarsky: J.A.M.A. 156:599-602, 1954.

MEDICAL SCIENCES REVIEWS

In the interests of continuing medical education, THE JOURNAL-LANCET *offers this department of authoritative reviews of important progress in scientific medicine, both in the fundamental and the clinical fields. The editors propose to define medical sciences very broadly, and hope that each subject treated will be of sufficient importance to interest every reader.*

Lipotropic Action of Choline in Liver Disease

WILLIAM E. CORNATZER, M.D.

Grand Forks, North Dakota

THE TERM "lipotropic" was first used in 1935 to describe the action of choline in the prevention and cure of fatty livers.[1] The materials which are physiologically active in removing fat from the liver were shown to be the lecithins, choline-containing phospholipides,[2] which make up part of the cell structure and are found in both cytoplasm and nucleus. The synthesis of these phospholipides is a primary function of all cells in the body. Mitochondria and large granules are very rich in phospholipides.[3] These intracellular units contain enzymes which can oxidize fatty acids and other metabolites.[4] The liver is the main source of plasma phospholipides,[5] which are not involved in fatty acid transport from the liver but show a direct reflection of the turnover.[6,7] Choline-containing phospholipides are probably an analytic part of an enzyme system necessary for the oxidization of fats and fatty acids. The lipotropic effect of lecithins appears to act on the metabolism of fatty acids in the liver, rather than enhancing their mobilization in the form of plasma phospholipides. There is a progressive decrease in the concentration of the choline-containing phospholipides in the liver and a diminished ability of the liver slices to synthesize these phospholipides in the dog maintained on a choline-deficient diet.[8] The addition of choline to the choline-deficient liver slices markedly increases the synthesis of choline-containing phospholipides.[8] Liver preparations from rats maintained on a low-protein diet produce less isotopic CO_2 from C^{14} labeled fatty acids than preparations from rats on adequate diets.[9] Supplementation of the low-protein diet with choline, or injection of massive doses of choline shortly before removal of the liver, greatly restored the ability of the tissue to produce $C^{14}O_2$ at a higher rate.[9] These findings suggest that the lipotropic effect of choline may result, at least to a large extent, from the enhancement of fatty acid oxidation in the liver. The composition of liver lipides can be altered by dietary intake of protein. There is usually a decrease in the level of total phospholipides in the livers of animals maintained on a low-protein diet.[10,11] The decrease is especially pronounced in the lecithin fraction, with a consequently lowered ratio of choline-containing to total phospholipides. Various studies comparing the rate of incorporation of radioactive phosphorus in the liver lipides of animals on various experimental diets have been made.[12,13]

Margaret J. Albrink[14] has shown that 70 to 80 per cent of the serum phospholipides of normal individuals are choline-containing and are within normal ranges in hepatitis and biliary disease. The first use of the radioactive phosphorus in studying phospholipide turnover was shown by Artom and associates in 1937.[15] Since then numerous studies have been made in experimental animals. No studies of phospholipide formation in human beings with liver disease were published until the works of Balfour[16] and Cayer and Cornatzer[17] were reported. Erf and Lawrence[18] recorded the amount of radioactivity in the plasma phospholipides in studies made on patients receiving therapeutic doses of P^{32}. In normal individuals, to whom radioactive phosphorus was administered, the radioactivity and the phosphorus level in inorganic and phospholipide fractions of the plasma were determined.[19] The phospholipide turn-

WILLIAM E. CORNATZER, *a 1951 graduate of Bowman Gray School of Medicine, is professor and head of the Biochemistry Department at the University of North Dakota and engaged in research sponsored by the Atomic Energy Commission, United States Public Health Service, North Dakota Cancer Society, and American Cyanamide Company.*

over, as measured in the plasma of normal individuals, varies widely but is rather constant in the same individual over a period of many months.[19] A correlation of the phospholipide turnover in both aspiration biopsy and blood plasma has been observed.[7] The plasma phospholipides appear to be a direct reflection of the turnover in the liver. The plasma phospholipide turnover, measured by radioactive phosphorus, was within normal limits in cirrhotic patients.[20] In patients with chronic hepatitis (Laennec's or atrophic cirrhosis) lipotropic deficiencies can often be demonstrated at the start of therapy.[21] In an acute exacerbation, the administration of a large dose of choline or methionine caused an increase in the synthesis of phospholipides.[20–22] Lipide phosphorylation is greatest in conditions in which a single dose of lipotropic agents is administered in the presence of "fatty" liver.[22] The effect of a dose of choline is chiefly due to the increased rate of formation of lecithins. The stimulating effect of various incomplete methylated ethanolamine derivatives was greatest in choline-containing fractions in rats maintained on a low-protein diet.[24] In cirrhotic patients, with fatty infiltration in the liver by biopsy, a signficant increase in the rate of phospholipide synthesis is usually demonstrated after a single dose of choline or methionine.[23] This stimulating effect of lipide phosphorylation by lipotropic agents is somewhat related to the previous diet, for it does not occur in experimental animals maintained on a stock diet[13] or in man on an adequate protein intake.[19] The synthesis of plasma phospholipides in the liver of normal individuals was further investigated to see if short periods of dietary regime could alter this function.[25]

The first observation that dietary protein influences the level of liver fat was indirectly made in 1935 by Best and Huntsman.[26] In 1939, Gyorgy and Goldblatt[27] reported that liver injury, in the form of acute diffuse necrosis, combined with fat infiltration, could be produced somewhat irregularly in young rats on a diet composed of 19 per cent casein. Gyorgy and Goldblatt[28] later demonstrated that cirrhosis could be produced invariably when the casein content of the former diet[27] was reduced to 10 per cent. Choline, methionine, and casein, either singly or in combination, prevented the development of experimental cirrhosis.[28–31]

In 1937, Patek[32] published the first series of papers on the treatment of a Laennec's cirrhosis with nutritional diets. The needle aspiration biopsy has proved an opportunity to study the actual histologic appearance in the liver under the influence of various nutritional states.[33] Beams[34] has shown that patients receiving methionine supplements show histologic changes in the needle biopsy and correlates with improvement in the clinical course. Franklin and associates[35] demonstrated, in a correlative study of the histologic response of fatty metamorphosis of human liver with lipotropic therapy, that the disappearance of fat in regeneration of the parenchymal cells were noted in all instances in a series of patients after lipotropic therapy. An adequate diet in protein has a sufficient lipotropic effect in alcoholic patients.[26] The addition of choline to an adequate diet did not yield additional effects over those observed with the diet alone. This is true in experimental animals, for an additional dose of choline to an adequate diet does not stimulate lipide phosphorylation. Phillips and associates[37] have shown that patients with cirrhosis on purified diets showed no change in hepatic functional tests or fat content during eight to ten days on the purified diet. However, after institution of the adequate diet for eight to ten days, an improvement in hepatic function occurred with a decrease in the hepatic fat on biopsy—apparently the quantity of precursors of choline. The methyl donors in the diet are the limiting factors in the prevention of fatty livers.[13] An adequate supply of proteins or choline will prevent fatty livers and will enhance the oxidation of fatty acids in the liver.[9] However, an additional large single dose of choline or methionine administered with an adequate diet to man[19] or experimental animals[13] does not stimulate lipide phosphorylation.

Recent experimental work indicates that choline administered orally to human beings is partly destroyed.[38] It has been demonstrated that approximately 50 per cent of choline taken by mouth is converted to trimethylamine by the bacteria in the gastrointestinal tract.[39] However, intravenous administration of choline in man did not increase the excretion of trimethylamine in contrast to choline administered orally. With intravenously administered choline, approximately only 9 per cent is lost in the urine of controls; whereas in acute hepatitis, but not in cirrhosis, this loss is almost double.[40] This observation of a decreased excretion of choline in the urine of patients with Laennec's cirrhosis[41] as compared with acute hepatitis is in line with the demonstration of an increase in lipide phosphorylation observed only in patients in whom fatty liver could be demonstrated. In patients with virus hepatitis, no lipotropic deficiency has been demonstrated and no alteration in the rate of phospholipide synthesis has been detected by the addition of methionine or choline in the treatment regime.[42]

The lipotropic action of choline is primarily involved in the mitochondria and large granules in the liver cell. Recent experiments demonstrate a progressive drop occurring in the lecithin P in the mitochondria and homogenates of the liver of choline-deficient animals.[43] The administration of a single dose of choline six hours before the animals were sacrificed produced a significant increase in the lecithin P of both mitochondria and homogenates.[44] This observation and that of Artom[9] indicates that mitochondria are primarily involved in the lipotropic mechanism of choline.

SUMMARY

The physiologically active units in removing fat from the liver are the lecithin molecules (choline-containing phospholipides). The cellular units, mitochondria and large granules, are very rich in phospholipides. In choline deficiency, a significant decrease results in the choline-containing phospholipides in the cellu-

lar fractions of the liver. The administration of a single dose of choline results in a pronounced increase in lipide phosphorylation in choline deficiency, as measured with radioactive P, and an increase in the choline-containing phospholipides of the mitochondria.

Liver from experimental animals maintained on a low-protein diet produced less isotopic CO_2 from C^{14} labeled fatty acids than preparations from animals on adequate diets. Supplementation of a low-protein diet with choline, or injection of a massive dose of choline shortly before the removal of the liver, greatly restored the ability of the tissue to produce $C^{14}O_2$ at a higher rate. It is suggested that the lipotropic effect of choline may result, at least to a large extent, from the enhancement of fatty acid oxidation in the liver.

Studies in animals have demonstrated that a pathologic picture resembling that of portal cirrhosis may be produced experimentally by various methods. In some instances, the use of lipotropic factors is of prophylactic and therapeutic value. This beneficial effect has been attributed largely to the stimulation of phospholipide formation (choline-containing phospholipides). In cirrhotic patients with fatty infiltration of the liver proved by biopsy, a significant increase in the rate of phospholipide turnover is usually demonstrated after a single dose of choline or methionine. This response to stimulation is no longer present after eight weeks of treatment when the liver fat has decreased or disappeared. In patients having cirrhosis without fatty infiltration and in patients with uncomplicated infectious hepatitis, the rate of phospholipide turnover is not stimulated by choline or methionine. Choline or methionine is indicated only at the beginning of treatment in patients with fatty infiltration of the liver who are actually ill and cannot eat. The same lipotropic effect is achieved more slowly with choline or methionine in patients who eat an adequate diet of protein-containing methionine (choline precursor).

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Hepatic disorders other than cirrhosis and portal vein disease may be indicated by esophageal varices. Of 62 patients with noncirrhotic liver disease, report Lt. Col. Eddy D. Palmer, M.C., U.S.A., and Irving B. Brick, M.D., of the Walter Reed Army Hospital and Georgetown University, Washington, D. C., varices were observed in 4 of 7 with chronic heart failure, in 8 of 14 with viral hepatitis, in 8 of 24 with simple portal fibrosis, and in 2 other cases. Portacaval anastomoses across the gastroesophageal junction may react to increased portal pressure by becoming varicose; however, these varices are not necessarily the cause of hemorrhage.

Eddy D. Palmer and Irving B. Brick: Am. J. Med. 17:641-644, 1954.

Lancet CLINICAL REVIEWS

This department of THE JOURNAL-LANCET *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Problem of the Asymptomatic Pulmonary Lesion

R. DREW MILLER, M.D.

Rochester, Minnesota

A 67-YEAR-OLD clothing salesman registered at the Mayo Clinic on November 11, 1953, for evaluation of an asymptomatic x-ray shadow in the field of the upper part of the left lung. The abnormal shadow had been discovered in June 1949 (figure 1*a*) in a routine roentgenologic survey. Follow-up roentgenograms were made in the next few months. Apparently little change occurred in the roentgenologic appearance of the lesion until August 1951 (figure 1*b*). In December 1951 the patient had a short episode of substernal pressure-type pain, which was relieved by pills and an injection. No apparent change was noted in the electrocardiogram to indicate localized myocardial injury. On January 23, 1952, he entered his local tuberculosis sanatorium and began to receive antimicrobial therapy with streptomycin and para-aminosalicylic acid. Use of the para-aminosalicylic acid was discontinued after four months, but the streptomycin was given for two more months. The roentgenologic appearance of the lesion showed little change during the six months of treatment, and the patient was dismissed for roentgenologic follow-up studies on an outpatient basis. The patient was not aware of any positive results of procedures for the detection of tubercle bacilli by smear, culture, or inoculation of guinea pigs with specimens of the sputum or with gastric washings. In September 1953, he had noted slight fever and cough of a few days' duration, relieved by injections of penicillin.

In October 1953, a follow-up roentgenogram of the thorax showed possible slight enlargement of the shadow under observation. Further investigation was recommended. There were no unusual symptoms at this time, however.

The patient was found to be an asthenic white man weighing 117 pounds, and 67½ inches in height. The blood pressure was 140 systolic and 80 diastolic, in millimeters of mercury. The cardiac rhythm was regular and there were no significant murmurs. Other than slight diminution of breath sounds and occasional soft râles over the left posterolateral aspect of the thorax, the findings were not significant. Lymph nodes were not enlarged.

Urinalysis, determination of hemoglobin, leukocyte count, and determination of the blood urea gave results within normal limits. The sedimentation rate was 15 mm. in one hour by the Westergren method. Result of the Kline test was negative. A tuberculin test, in which 0.0001 mg. of purified protein derivative was used, was reported as giving a negative result. A second injection of 0.005 mg. of purified protein derivative was reported to have produced a positive reaction after forty-eight hours. Results of a skin test with histoplasmin were reported as 4-plus after forty-eight hours. An electrocardiogram showed only left axis deviation. Examination of the sputum, bronchial smears, and bronchial washings for malignant cells and acid-fast bacilli gave negative results.

A roentgenogram of the thorax showed a rath-

R. DREW MILLER, *a 1946 graduate of Northwestern University Medical School, is consultant in internal medicine and diseases of the chest at the Mayo Clinic and instructor in internal medicine in the Mayo Foundation.*

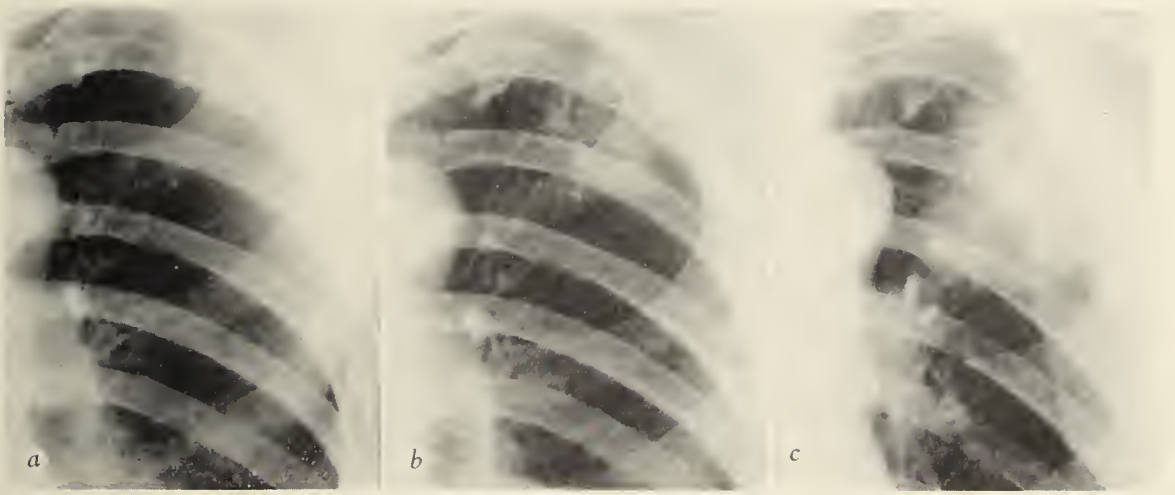

Fig. 1. Localized views of shadow in the field of the upper part of the left lung field: *a*, June 1949; *b*, August 1951; and *c*, November 1953.

er extensive lesion on the left at the level of the first and second anterior interspaces (figure 1*c*). Tomograms of the area showed no definite cavitation. The serial roentgenograms of the thorax made in the patient's home town, when reviewed, showed very slight enlargement of the shadow over the two-and-one-half-year period. Bronchoscopy revealed no gross abnormalities.

Because of the indeterminate nature of the lesion after clinical study and observation, left thoracotomy was advised. A grade 3 adenocarcinoma of the posterior segment of the upper lobe of the left lung was found at operation, with no involvement of the hilar nodes. Left pneumonectomy was performed. The patient made an uneventful recovery.

Follow-up reports from the patient's local physician indicated that symptoms of cerebral metastasis appeared. The patient died on June 5, 1954. A large metastatic lesion of the right cerebral hemisphere was found at necropsy.

COMMENT

The value of survey roentgenograms, which is widely appreciated among the laity as well as within the medical profession, is again demonstrated in this case. The case further points out the difficulty so often encountered in making a clinical diagnosis after an asymptomatic lesion is discovered. The lesion located peripherally in the field of the upper part of the left lung had characteristics of either a chronic inflammatory process or a neoplasm. Although it was possible to detect the abnormality by means of the roentgenogram, the roentgenogram did not provide the etiologic diagnosis. Laminated calcium, diagnostic of a granulomatous process, was not evident in any of the serial thoracic roentgenograms of this patient. Even tomograms, made just before operation, did not demonstrate calcium. Thus, a malignant neoplasm could not be ruled out from a roentgenologic standpoint. The value and limitations of roentgenologic technics in the detection of asymptomatic lesions have been reviewed by Good and associates.[1] Serial roentgenograms showed little change in the abnormal shadow. Although failure of such a shadow to change might suggest that the lesion thus depicted is benign, this case demonstrates how a bronchogenic carcinoma, particularly an adenocarcinoma, may show little change over a period of months or even years.

The failure of previous bacteriologic studies by home physicians to demonstrate tubercle bacilli in the patient's sputum or gastric washings cast doubt upon the clinical diagnosis of pulmonary tuberculosis. Furthermore, failure of the shadow to regress during combined chemotherapy should lead to further questioning of the previous clinical diagnosis. The skin tests indicated that the patient previously had been infected with tubercle bacilli and probably also *Histoplasma capsulatum*, but additional bacteriologic studies had failed to show that the pulmonary lesion was related etiologically to the cutaneous reactions. In this case a clinical diagnosis could not be made by the usual laboratory methods, and thoracotomy became necessary. The incidence of malignant lesions among asymptomatic circumscribed pulmonary lesions has been pointed out by Harrington.[2]

The patient's ultimate clinical course illus-

(Continued on page 44A)

Newer Concepts of the Causes and Treatment of Diabetes Mellitus, 1954. Proceedings of the Symposium on Diabetes sponsored by the New York Diabetes Association and held at Memorial Hospital and The New York Academy of Sciences, New York City: National Vitamin Foundation, Inc. $2.50.

The book includes 13 review papers on basic biochemical and clinical studies regarding advances on the action of hormones and the current treatment of diabetes mellitus.

The first section — biochemical — thoroughly reviews the hereditary factors of obesity as related to diabetes mellitus, the action of insulin in vitro, the effect of hormones on intermediary carbohydrate metabolism, and the site and action of glucagon. The second section — clinical — reviews the management and control of diabetes mellitus with and without such complications as pregnancy and infection. An important review regarding the present day lack of an adequate nutritional intake merits detailed reading.

The book is on selected topics of fundamental biochemistry as well as its clinical application. It is a book to be recommended to all those interested in diabetes mellitus.

DONALD S. AMATUZIO, M.D.

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The Nursing of the Elderly Sick: A Practical Handbook of Geriatric Nursing, by T. N. RUDD, M.D., 1952. Modified and revised by ETHEL JOHNS, R.N., 1954. Philadelphia: J. B. Lippincott Co. 100 pages. $1.25.

The original edition of this excellent little book was written by Dr. Rudd for use in Great Britain. This new American edition has been revised by Ethel Johns, R.N., for use on this side of the Atlantic by modifying the language to conform to our customs, climate, and nursing organization.

The volume is eminently practical, warmly understanding, and surprisingly comprehensive. It does not attempt to repeat the basic fundamentals of good nursing, for these are readily available in many excellent general text books on nursing. However, it covers thoroughly the *special* nursing problems encountered in caring for the aged sick, including mental aberrations, nutrition, incontinence, protection from injury, pre- and postoperative care of the aged surgical patients, and the fundamentals of rehabilitation. The material is so well presented that it should

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be invaluable to those families who must take care of the infirm and disabled aged at home. It is also recommended as *must reading* for all nursing home operators, their nursing staffs, and as supplementary reading in all nursing schools. The staffs of chronic disease hospitals and rehabilitation centers can profit immensely by careful study of its contents. We welcome it as a most significant addition to our armamentarium in fighting the prolonged nursing so frequent in infirm old age.

EDWARD J. STIEGLITZ, M.D.

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A History of Medicine, by RALPH H. MAJOR, M.D., 1954. Springfield, Illinois: Charles C Thomas, 2 volumes, 1,155 pages. $14.50.

A genuine treat is in store for those physicians who read these volumes. While some practicing physicians in the past have found allotment of time for any such reading difficult, others have found such reading, on account of its content and method of presentation, very rewarding.

Those who have special interest in the history of medicine will undoubtedly find new material, although the author states that the book was not written for the specialist in medical history but "primarily for the medical student and the medical practitioner in an attempt to interest them in the history of their own profession, which, in spite of attacks and abuse, quacks and charlatans, and in spite of its own mistakes, has proved itself more enduring than any of the civilizations which gave it birth." Throughout this work from primitive times to the present, discussion of medicine has been linked to contemporary civilization, so that from this book stems a broader appreciation of many world cultures.

During several trips to Europe, Dr. Major checked many sources of material and has been aided by his reading knowledge of Latin, French, German, and Italian. Those of us who have been fortunate enough to know Dr. Major as a teacher recognize his clear and concise expression and his capacity to convey the fruits of his investigations to others. Unusual pains have been taken by the author to insure the validity of the text.

The author has used a plan of following the principal streams of medical thought as shown in the biographies of important figures within and without medicine who have a significant place in medical history. Biographic addenda are given after the main chapters with a general bibliography at the end of volume 2. The work is profusely illustrated, and the volumes would grace any physician's library.

C. A. MCKINLAY, M.D.

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Clinical Genetics, edited by ARNOLD SORSBY, 1953. London: Butterworth and Co., and St. Louis: C. V. Mosby Co. 580 pages. $17.50.

This is one of the most attractive books on clinical genetics that we have seen, filled as it is with detailed information from the literature and from the experience of the several men who have contributed the chapters. Many of these men are from England, Scotland, Switzerland, and the Scandinavian countries, but there are several chapters by the American leaders in the field of human genetics. Most of the information is in regard to diseases other than mental, but there is a good chapter on mental disease written by Slater.

This book should certainly be on the shelves of every man who is interested in genetics. Particularly interesting to the reviewer were the sections on the probability that quite a number of diseases are not due to any one dominant or recessive gene but to the concerted action of many. With the help of some calculations based on Kallmann's work, Eliot Slater concluded that schizophrenia might be due to the associated action of some 125 autosomal and recessive genes.

WALTER C. ALVAREZ, M.D.

•

Manual of Antibiotics, edited by HENRY WELCH, 1954. New York: Medical Encyclopedia, Inc. $2.50.

The contents of the text are lists of antibiotics with the trade names given by each pharmaceutical company. The book has little or no value to the physician except as a reference encyclopedia. The busy pharmacist may find it of value.

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American College Health Association News . . .

NEW MEMBERS

We are happy to welcome 4 new members whose applications have been approved by the Executive Committee:

California State Polytechnic College, Kellogg-Voorhis Campus, San Dimas, California
Representative: Robert D. Shaver, M.D.
Drake University, Des Moines, Iowa
Representative: Mary R. Caron, R.N., M.A.
Niagara University, Niagara Falls, New York
Representative: Peter J. Iannuzzi, M.D.
University of Toledo, Toledo, Ohio
Representative: Horace G. Gordon, M.D.

° ° ° °

SECTION ACTIVITIES

Information from Richard G. Bond, public health engineer of the staff of the Health Service at the University of Minnesota, advises that the second National Conference on Campus Safety is to be held at the University of Minnesota April 18 to 20, 1955 at the Center for Continuation Study. The program will be devoted to aspects of campus safety relating closely to environmental health programs of college and university health services in addition to conventional subjects of campus safety. Further details may be obtained from Mr. John Morris, safety supervisor, Students' Health Service, University of Minnesota.

The 1955 meeting of the Michigan College Health Association has been announced for May 27 at the Student Union, Michigan State College, East Lansing, Michigan, by Dr. Olga Sirola, president. The theme of the meeting will be "The College Administrator's Responsibility for Health of Students." Representatives of other sections are cordially invited to attend.

A corrected list of the officers of the Ohio Section for 1955 has been received. They are as follows:

President, Dr. Eleonora L. Schmidt, Ohio University; vice president, Dr. Karl H. Feistkorn, Ohio State University; and secretary-treasurer, Mrs. Ruth Dutton, R.N., Miami University.

Officers of the Pacific Coast Section for 1954-1955 elected at the meeting held December 3 and 4, 1954 are:

President, Dr. Charles N. Lester, University of Washington; president-elect, Dr. Glen R. Leymaster, University of Utah; secretary-treasurer, Mrs. Ruby Rich Burgar, R.N., Occidental College; member at large, Anita D. Laton, Ph.D., San Jose State College.

Section refunds will be made by the secretary-treasurer of the A.C.H.A. to all sections upon notification by the president or secretary of the section of the time and place of the section meeting and the number of colleges enrolled in the section. The constitution of the A.C.H.A. permits a refund to each section of $2.00 per year for each member of the local section who is also a member of the national association, if the section is active.

° ° ° °

PERSONNEL

Dr. Wm. Goodricke Donald, director of the Student Health Service of the University of California at Berkeley has announced the appointment of Dr. John W. Brown, formerly director of the Health Service at the University of Wisconsin, to his staff as consultant in industrial health.

(Continued on page 40A)

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(Continued from page 36A)

Dr. J. H. Means is acting medical director of the Health Service at the Massachusetts Institute of Technology, replacing Dr. Dana Farnsworth who is now director of the Health Service at Harvard University.

Dr. Francis W. Logan has been appointed director of the Student Health Service at Ohio Wesleyan University at Delaware, Ohio. He assumes the duties carried for so many years by Dr. George Theron Blydenburgh who died January 22, 1954. Dr. Logan graduated from the University of Illinois College of Medicine, and, after practicing for many years in Mishawaka, joined the University of Illinois Student Health Service.

Dr. C. G. Menzies, director of the Student Health Service at Michigan State College at East Lansing has announced 2 new members of his staff. Dr. Ralph H. Ruhmkorff has been appointed assistant director. Dr. Ruhmkorff has been a member of the staff of Michigan State College Health Service since 1948. Dr. George J. Andros, formerly assistant professor in Obstetrics and Gynecology at the University of Chicago joined the staff December 1, 1954.

Mr. Richard G. Bond has added 2 new members to his staff in the division of environmental health in the Students' Health Service of the University of Minnesota. Mr. Ralph O. Wollan, health physicist, formerly at the Oak Ridge National Laboratories will serve as the radiological safety officer for the university. Mr. John Morris, previously supervising safety engineer with an insurance company in Detroit, will develop a safety program for university students and staff members.

Mrs. Ruby Rich Burgar, R.N., secretary-treasurer of the Pacific Coast Section, has informed us of the death of Reverend James Joseph Lyons, S.J., in San Francisco on October 22, 1954. Father Lyons had been a member of the executive committee of the Pacific Coast Section.

EXPANSION PLANS

Word has been received from Dr. R. M. Taylor of Wittenberg College, Springfield, Ohio, that an addition is being planned to consolidate the Health Service facilities. The addition is to include nurses' quarters, service rooms, kitchenette, and the infirmary.

News Briefs . . .

North Dakota

The Craven-Hagen Clinic, oldest medical group in continuous service to residents of Williston and the surrounding area, opened its quarters on the second floor of the new Rolfstad Building January 31. Space is designed to serve a clinic group of 5 or 6 physicians. Facilities include 5 consultation rooms and 15 examining rooms. The middle court houses the business office, medical secretary's quarters, nurse's station, modern laboratory and x-ray facilities, minor surgery and recovery rooms, and the physical therapy unit. A doctor's lounge, nurse's lounge, and library are in the rear.

* * * *

Open house was held recently to mark the opening of the new Lisbon Clinic. The 13-room floor plan and unfinished basement allow space for ample expansion. The clinic includes offices of Drs. A. K. Lews, Paul Walter, and A. L. Pushor, doctors responsible for erection of the new building.

(Continued on page 45A)

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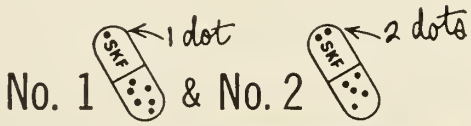

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Patent Applied For

USE OF COBALT AND IRON IN TREATMENT AND PREVENTION OF ANEMIA OF PREMATURITY

(Continued from page 82)

lytic action enabling available iron to be more readily utilized for hemoglobin synthesis.

This work was carried out under a grant from the Endowment Fund of the Royal Free Hospital (London). We are grateful to Dr. Ian Sutherland of the M.R.C. Statistical Research Unit for his statistical analysis of our results.

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(Continued from page 119)

trates the serious complications which often follow the discovery of bronchogenic carcinoma, even though the hilar nodes were not involved. Tinney and Moersch[3] found symptoms referable to the nervous system in 12 per cent of 448 cases of carcinoma of the lung. In 4 per cent of the entire series, the neurologic symptoms represented the presenting complaint. King and Ford,[4] in reviewing 100 cases of metastasis to the central nervous system from carcinoma of the lung, concluded that these types of metastasis occur early and frequently. This further demonstrates the importance of early diagnosis and treatment of asymptomatic lesions of the lung.

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The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA,
NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

FOREWORD . . . .

I THINK IT IS SIGNIFICANT that the two articles devoted solely to tuberculosis in this year's April issue are both concerned with results of tuberculin testing programs. With the tuberculosis death rate continuing its gratifyingly sharp decline, the tuberculin reaction is becoming increasingly important in differential diagnosis. Furthermore, to the public health administrator, it is becoming increasingly important as an index of the extent and location of the remaining tuberculosis problem, and the progress being made in actual eradication of tuberculous infection from the population.

The articles on x-ray in diagnosis, and on the incidence of bronchogenic carcinoma reflect the importance of differential diagnosis when the physician is confronted with a patient suspected of having tuberculosis or some other pulmonary disease. I think it is interesting and a tribute to our medical profession that in this country the designation "phthisiologist," indicating a physician specializing in tuberculosis, is seldom, if ever, heard. A physician cannot really be a clinical specialist in pulmonary tuberculosis without being a specialist in all other pulmonary pathology – and, indeed, without being a specialist in all aspects of internal medicine.

The article on health problems in Europe is of interest. Except for southern Europe, the control of tuberculosis on that continent has pretty much kept apace with that in the United States, but considering the world as a whole – and especially those countries in the tropical belt – such is not the case. In connection with a meeting last year sponsored by the National Citizens' Committee for the World Health Organization, I had an interesting informal discussion with several distinguished physicians extensively involved in international health activites, including a nutritionist and a malariologist. The group agreed, that with the tremendous strides made recently in preventing malaria, tuberculosis is probably unchallenged as the most important specific communicable disease problem in the world today. But the discussion also brought out the intimate relationship of the various communicable diseases to each other, and to the social and economic status of the population. Malaria, for example, may keep the farmers from harvesting their crops. Malnutrition, resulting from the crop failure, increases susceptibility to tuberculosis and causes further spread, which in turn further prevents the wage earner from providing adequately for his family. Thus, in the public health field, as in the diplomatic field, we are impressed with the complex interrelationships in this shrinking world.

JAMES E. PERKINS, M.D.,
Managing Director, National Tuberculosis Association

Public Health, Public Relations, and the General Practitioner

WALTER C. GRAY, M.D.

St. Louis, Missouri

Since the inception of the American Academy of General Practice several years ago, the general practitioner has staged a rather spectacular comeback in the field of American medicine. Much attention has been directed toward his postgraduate education to increase his medical efficiency and vigorous attempts have been made to give him better public relations both in the field of medicine and with the American public. These efforts from a public relations standpoint are quite commendable. The favorable publicity is long overdue. I feel that the role of the general practitioner in the field of medicine is a major one, but I likewise feel that the average general practitioner is not completely aware of the importance of his role as a leader in civic and community affairs.

During the past two years the St. Louis Academy of General Practice has engaged in a public health program in the form of tuberculin patch testing of school children in St. Louis County. The results from a public health standpoint have been excellent, but the results from a public relations standpoint have been nothing short of spectacular. It is hoped that a portrayal of the work done by the St. Louis Academy members may act as a guide to other general practitioners throughout the country, indicating to them how they can improve public relations in their communities and at the same time do a tremendous job in the field of public health. The details of this program will be found in an original article soon to be published in the *Journal of the American Medical Association.* Therefore, this article will concentrate on public relations and public health.

When Dr. J. Arthur Myers of Minneapolis spoke before the St. Louis Academy of General Practice in September 1951 on tuberculin testing in Minnesota schools, he aroused a spark of enthusiasm among the members which later blossomed into one of the most intensive case-finding programs that this country has ever seen. The members were quite enthusiastic, and in January 1952 the Tuberculosis Committee of the St. Louis Academy of General Practice sent letters to all members urging them to patch test patients in their private practice with patch tests furnished by the Tuberculosis and Health Society of St. Louis. Distribution was accomplished through the Retail Druggists' Association. Although there was much initial enthusiasm, the individual members never seemed to get around to patch testing large numbers of their patients. This was not due to a lack of sincerity on the part of individual members, but merely due to a lack of organization. I felt that we were missing a great opportunity to accomplish a sizable job in tuberculosis case finding and the idea was presented to a new Chamber of Commerce in Northwest St. Louis County for mass tuberculin patch testing in their school district. The Health Committee of the local Chamber of Commerce acted as a liaison group with the School Board, and worked out plans and obtained permission for patch testing all the school children in the Ritenour school district. Since the program was the first of this kind, we encountered many difficulties in methods, technic, organization, and public relations. The Tuberculosis and Health Society health education workers gave talks to all the school children and to some of the parent groups and 85 per cent of the children in the school district were patch tested, or 3,950 children. Another 1,200 children were patch tested in Presentation and St. Ann's schools, making a total of 5,150. Out of this number, 204 were found to be reactors and all of them were referred to the County Health Department or their private physicians for x-ray films, with their parents and any other members of the household over the age of 15 as contacts. Of the reactors and contacts who were x-rayed, 5 parents were found to have active tuberculosis. With these rather unexpected results, the Patch Testing Committee of the Academy met with the Tuberculosis and Health Society and the Cham-

WALTER C. GRAY, *a 1943 graduate of St. Louis University School of Medicine, is chairman of the Committee on Tuberculosis of the St. Louis Academy of General Practice, St. Louis, Missouri.*

ber of Commerce during the summer months to work out a more comprehensive program which would govern all future patch testing activities of the Academy. The following fall 618 children from a school at Jefferson Barracks were patch tested and 1 child of 6 years of age was found to have active tuberculosis.

In the original program in the Ritenour School district, the teachers applied the patch tests. A note was sent home with the school children for the parents to remove the patch tests two days later, and on the following Monday morning, four days after application, the teachers screened the school children for any signs of red marks on their backs. All those who were suspicious were sent to my office to determine whether they were reactors. The fact that the school teachers were asked to apply the test led to some rather poor public relations in the initial program because they felt they were being asked to assume a medical responsibility. They also felt that the general practitioners in the neighborhood could have been more competent, both by applying the test and by talking to the parents and teachers to give them more information on the purpose of the testing program. With this in mind, subsequent programs have been accomplished with members of the Academy applying all tests and returning four days later to read them. We have found this procedure to be one of the best public relation factors in the whole program. The fact that members of the Academy talk to the Parent-Teachers Association whenever possible before a testing program is carried out, plus the fact that whenever possible the general practitioner gives the children orientation sessions prior to testing, has shown members of the community that the general practitioner is the man they can look to for a sincere interest in public health problems. More and more the Academy is being called on by various groups in the community for advice on public health matters and public health programs which are initiated by service organizations in various communities.

I do not mean to imply that the St. Louis Academy of General Practice is the only organization active in tuberculin testing in the county. The St. Louis County Health Department had embarked on a testing program of its own in some of the contract schools on a smaller scale prior to the initiation of the original program in the Ritenour district. For awhile the Academy and the County Health Department seemed to be at cross purposes insofar as their programs were concerned. So, a series of meetings were arranged with the County Health Department, members of the Academy, and members of the St. Louis Tuberculosis and Health Society, to work out a joint plan for tuberculin testing in St. Louis County to avoid duplication of results and to try to establish an over-all coordinated program involving the 3 groups. Much of the success of these meetings was due to the wonderful spirit of cooperation exhibited by Miss Ellen Boyce, executive secretary of the St. Louis Tuberculosis and Health Society, and Dr. John Murphy of the St. Louis County Health Department. After a series of 3 or 4 meetings, during which various phases of the program were discussed, a well-coordinated community project was underway. Not counting children from various parochial schools who have been tested, of the 77,148 school children in public schools in St. Louis County, 39,632 have been tested during the past two years. The St. Louis Academy of General Practice tested 22,628 and the County Health Department tested 17,004. This leaves 37,576 children to be tested, and we hope to accomplish this task within the next two years. A long-range program has been set up which includes initial testing of all school children in public and parochial schools in St. Louis County plus two follow-up programs. The St. Louis County Health Department is concentrating on several school districts and plans to test the entire school population in these school districts on a yearly basis in an attempt to determine how many become positive converters from year to year, hoping also to shed some light on the accuracy of the patch test as a screening method. The St. Louis Academy of General Practice, because of limited manpower at present, plans to retest all school districts and schools that have been tested in the last two years. Using a spot-check method, they intend to test the first, fifth, and ninth grades, and all newcomers to the school district, not including kindergarten students, in order to see how many children in the original test program become positive converters later. With over 100,000 school children in the fastest growing suburban area in the United States, this becomes a monumental task. But we feel that the Academy will grow as the county grows and hope that we will be equal to the task.

In order to give a better idea of the scope of this program which started less than two years ago, here are a few interesting figures:

June 1954	
St. Louis City School System	1,595
Academy of General Practice	5,270
County Health Department	6,423
Independent	2,467
Total	15,755

Out of this group, 658 were positive reactors, all of whom were x-rayed with enough contacts to make a total of 1,395 reactors and contacts x-rayed. There were a total of 13 cases of active tuberculosis in 8 adults and in 5 children, and an additional 12 suspicious lesions to be x-rayed at regular intervals.

So a program sparked by the Academy of General Practice, although the academy members had only tested 5,270 children, started a county- and city-wide program which was responsible for 3 times that number of tests. Even more surprising are the following figures:

JANUARY 14, 1955

St. Louis City School System	9,561
Academy of General Practice	29,027
County Health Department	23,742
Independent	4,131
Total	66,461

Note that these results occurred only eighteen months after the initial program in Ritenour School district. The program has caught on and the rate of testing has been accelerated by all 3 groups to the point where it is no longer possible to give the latest figures. My estimate at present writing, and this is purely a guess, is that approximately 66,000 school children have been tested in St. Louis and St. Louis County in the past two years.

I know that I am perfectly safe in stating that the program will enlarge even more rapidly in the months to come if only because of one fact. We have found that whereas men were at one time reluctant to give their time to this program, either because of inexperience or because they felt it was not worthwhile, after a man has taken part in the program, he is ready to do even more when asked again. The enthusiasm and sincerity of the men who take part in the program is rather contagious, and a program which at one time was strictly an orphan is now an accepted public health procedure in this area. My fondest hope is that tuberculin patch testing of school children will someday become an accepted standard program in all public and parochial schools in St. Louis and St. Louis County. I feel that when that day comes, a very important step will have been taken toward the eradication of tuberculosis from our community.

As mentioned before, in our first 1,395 positive contacts and reactors x-rayed, 13 cases of active tuberculosis were found, giving us a case-finding rate 10 times that of the national average with the Mobile X-ray Unit as a method of case finding. This fact was mentioned in the original article for the *Journal of the American Medical Association,* but it was also mentioned with a word of caution that nothing was predicated on such a small number of cases. It was felt that we did not have enough cases for a really analytical survey, and apparently this was all too true. Final figures are not available for the first 50,000 cases, but I am sure from a preliminary survey of our figures that the average case found per 1,000 children patch tested will not approach the figures obtained in the first 15,000. The County Health Department in a recent survey brought to light one of the reasons. It announced that the Overland district, which is in the middle of the Ritenour School district, has the highest tuberculosis rate according to their 70 mm. x-ray survey of any community in St. Louis County. Since the first 5 cases were found in this community in the first 5,000 school children patch tested, it is quite conceivable that we were operating in a hot spot insofar as tuberculosis incidence is concerned without being aware of it, but this, too, we feel has been a valuable service to the community and to the county as a whole if only in pointing up the need for more concentrated effort in the form of x-ray surveys in this particular community. At a recent meeting with the Health Department, the Mayor of Overland and the St. Louis Tuberculosis and Health Association, a comprehensive concentrated program for x-raying as many members of the community as possible was outlined. After this survey, we hope to have a little better idea of how much weight to give the figures of our testing program in this community.

At this point you may well wonder what possible relationship the foregoing has to the title of this article. I shall attempt to summarize the contents to show that relationship. First of all, here is a program of tuberculosis case finding which was instituted by the general practitioners of the community in cooperation with the Tuberculosis and Health Society. The County Health Department and the City Public School System had already experimented with the program and did not feel that it had much merit, but upon seeing the results of the first 5,000 patch tests in the Ritenour School district, the County Health Department reversed its opinion or at least reserved its judgment and carried on an accelerated patch test program of its own. When we seemed to be at cross purposes with the other agencies, conciliatory meetings were held and all difficulties were ironed out until we now have a comprehensive Community Health Program with a single set of standards, a single set of forms, and everyone cooperates in true commu-

(Continued on page 39A)

Present Concepts in the Treatment of Asymptomatic Tuberculosis

ROBERT E. RYDELL
Minneapolis, Minnesota

Several groups in the United States today are instituting antimicrobial drugs in the ambulatory treatment of asymptomatic primary tuberculous infections if the infection is known to be in a "recent tuberculin converter." The term "recent converter," as used in this paper, means that, in a given individual the tuberculin reaction is known to have changed from negative to positive within a preceding period of three months or less.

Use of drugs in the asymptomatic recent converter had been considered in relation to both the early tuberculostatic sulfanilamide derivatives and streptomycin alone, but these drugs had limitations which precluded their use in such a program. However, with the discovery of new effective drugs, especially isoniazid, and ways to slow down the rate at which the bacilli become resistant to the drugs, some of the earlier objections to such early treatment have been overcome.

Much of the recent interest has been stimulated by the enthusiasm of Waring.[1] In a recent article he strongly advocates the concurrent use of all the 3 potent antimicrobial drugs generally utilized today – isoniazid, para-aminosalicylic acid, and streptomycin or dihydrostreptomycin – to be instituted immediately in the recent converter and to be continued for at least six months. Bed rest is used only when there is some evidence of toxicity from the tubercle bacillus.

Adams[2] has set up a study, currently in operation, to detect and treat primary tuberculosis in the earliest possible phase. The persons in the study are exposed infants, children, and adults who are followed by frequent tuberculin testing. A system has been worked out whereby either an experienced public health nurse or a physician applies the intradermal skin test and reads it at seventy-two or ninety-six hours. The persons who react negatively are retested at monthly intervals. Any person known to have converted within a period of one hundred days is considered suitable for therapy with isoniazid, 5 mg. per kilogram of body weight per day – maximum total of 300 mg. per day – for six months. The candidates for treatment are divided by random sampling procedures into a group receiving treatment and a control group receiving no treatment. All converters, wherever possible, receive special roentgenologic examinations and are tuberculin tested every six months. A proper dilution is used to avoid excessively severe reaction. The rate of complications and reconversions are carefully recorded. In addition, a laboratory study in which guinea pigs are used and following closely the lines of the clinical study is to be conducted.

Another study to evaluate the effects of early treatment of primary tuberculosis with drugs is currently being conducted by the United States Public Health Service[3] with the cooperation of Lincoln and some 20 other pediatricians located throughout the United States. All infants with positive tuberculin reaction and all children more than 2 years of age through 15 years of age with a positive reaction plus some roentgen evidence of primary disease, which means, essentially, a suspicious infiltration on a chest x-ray film, are divided into a control group receiving a placebo and a group receiving isoniazid for an extended period. The physician himself does not know in which group any given child has been placed. To be sure a child receives isoniazid, in case the attending physician expresses concern over developments while the child is receiving an unknown medication under the program, he immediately starts treatment from a supply that he knows is isoniazid and that is so labeled.

Myers[4] and several other authorities in the field of tuberculosis have expressed their willingness to use either streptomycin in combination with para-aminosalicylic acid or isoniazid, alone or together with PAS, in the recent converter.

Many others, perhaps the majority, do not institute treatment with the presently available

ROBERT E. RYDELL *is a member of the June 1955 graduating class at the University of Minnesota Medical School.*

drugs in such early treatment. Still others treat the recent converter only under specific circumstances; for example, the infant or adolescent, periods of life known to be especially dangerous.[5,6]

Because of the lively interest and apparent difference of opinion concerning such early treatment, a brief review of the background material and information is presented. Theoretically, the success of and need for such a program is based on 4 basic premises: (1) that we possess a specific test that enables us to detect an early lesion, (2) that the pathologic changes at the time we are able to detect the disease are compatible with (3) a specific therapeutic regime for which we can have reasonable hopes of success without severe untoward effects, and (4) that such a program is needed, either on the basis of immediate danger or from subsequent "endogenous" reinfection.

In the reaction of the animal body to tuberculin, we have a very specific test that tells us within a restricted time interval when initial infection has occurred. Extensive experience with reactions to tuberculin in animals, especially cattle, has led not only to the pathologic demonstration of tuberculosis in all but an insignificant percentage of the reactors, but also attests to the sensitivity of this test.[7] The high degree of success in tuberculosis control programs in cattle, using this reaction as the sole diagnostic weapon, proves that few infective animals are nonreactors.

The same situation holds true in human tuberculosis. Even though "tuberculin negative tuberculosis" does occasionally occur,[8] Furcolow[9] points out that, except in overwhelming infection, a negative tuberculin reaction occurs in less than one-half of one per cent of all proved cases of tuberculosis. The time interval elapsing between exposure to virulent bacilli, development of infection, and subsequent skin reactivity to tuberculin varies from three to seven weeks in the infant.[10,11] In the occasional case in adults, it appears that a similar time interval for the development of sensitivity is required. The majority of authorities assume that the loss of tuberculin skin reactivity occurs in the absence of continued exposure, internally or externally, to the bacillus.[12] Furcolow[9] quotes Dahlstrom as stating an incidence of 2 per cent reconversions in untreated asymptomatic reactors to first-strength tuberculin and 60 per cent reconversions in those reacting only to second-strength tuberculin. He further states that this is consistent with his own experience.

The "false-negative" reaction to tuberculin is not understood. As Dubos[13] has recently stated, more accurate knowledge regarding the specificity of the tuberculin reaction and the meaning of a persistently positive test is not known. How the reaction is influenced by the physiologic state of the individual is likewise unknown. The relation of allergy, as shown by a positive and very occasionally even a negative reaction, to immunity factors is not understood. It is reasonable to conclude, however, that in the tuberculin reaction we have a very specific test that, in all but an insignificant percentage of persons, can tell us within a period of a few weeks whether initial infection has occurred. The lesions must necessarily be young in terms of time, if not extent, when conversion occurs.

The fundamental early processes involved in the primary infection by the tubercle bacillus appear to be well worked out and adequately documented.[14–19] The bacilli from any portal of entry rapidly gain entrance into the blood stream and are disseminated widely throughout the body. Numerous small foci of inflammation result. The number of such foci is variable, and the fate of each focus is uncertain. Some undoubtedly are completely resolved and others go on to develop into characteristic late lesions. The pertinent facts about the early lesions that concern us now are few. Although necrosis can and does occur early, the necrotic foci are usually of microscopic size until allergy develops. If large areas of necrosis develop at this time, the disease most likely becomes clinically evident. The usual course is development of a localized cellular response sufficient to contain the spread of the lesion. The remaining fact of importance is that definite fibrous encapsulation of the tuberculous focus does not occur until after the fourth to eighth month. Therefore, in the absence of symptoms, the early tuberculous lesion is relatively small and not protected by anatomic barriers that would prevent diffusion of blood-borne substances into the lesion. The great majority of early lesions harbor viable bacilli.

The morphology of older lesions has been worked out as well.[17,18] The changes consist primarily of continued organization of the lesion with deposition of calcium salts and even bone formation in a high percentage of cases. Eventually, reabsorption of variable degrees occurs in many of these lesions. It is known that viable tubercle bacilli can be found in tubercles as old as 15 years of age. The percentage of lesions from which bacilli can be cultured varies greatly, decreasing rapidly with time.[20,21] The

significance of an old primary lesion as it relates to later elinical disease remains a disputed area.[12, 22–24]

Dubos[25] has east much doubt on the efficiency of standard baeteriologic methods in recovering eultures from old lesions, and the pathogenicity of bacilli recovered by culture remains an unelarified area. Suffiee it to say that about all we ean eonelude is that viable bacteria ean remain in old primary lesions for eonsiderable periods of time and that reabsorption on a lowered host resistanee eould eonceivably cause reinfeetion. The presenee of old primary lesions in the eentral nervous system appears to be elosely related to late tubereulous meningitis.[26]

The drugs whieh have been suggested for use in the asymptomatie recent eonverter include, as previously mentioned, isoniazid, streptomyein or dihydrostreptomyein, and para-aminosalieylie aeid. Isoniazid is the preferred drug, either alone or in eombination with para-aminosalieylic aeid, for reasons whieh will be mentioned. It is known that streptomyein does not appear to have any effect in hastening the resolution of a primary lesion; and, in addition, complieations in bones, lymph nodes, other organs, and even meningitis ean develop and progress while the patient is under continuous streptomyein therapy.[27] There is as yet no evidence that isoniazid hastens the resolution of primary pulmonary lesions either, but the hazard of tuberculous meningitis is reduced to a minimum. Lincoln states that she has neither seen nor heard of a ease of meningitis developing in a patient while under treatment with isoniazid, even though the tubcrele baeillus could be cultured from the cerebrospinal fluid. So impressed is she with this observation and so grave is the mortality and morbidity from this eomplication that, on this evidenee alone, she suggests the use of isoniazid in infants who are recent converters even though they remain asymptomatic.

Numerous observations in human and experimental tubereulosis have shown clearly that the known specifie antimicrobial drugs fail to kill all the bacilli in infeeted tissue, either intra- or extraeellular. After a summary of sueh observations, Dubos[25] concludes "All these facts leave one with the impression that no teehnique is as yet available to bring about with eertainty a complete eradieation of the bacilli from infected tissues — after antimierobial drugs have ceased to exert their restraining influenee on infection, either because the infeetive organisms have become resistant to them, or because therapy has been interrupted. Only the resistance of the host can act as a brake on reaetivation of disease caused by the bacilli surviving here and there, in one form or another, detectable or not by the classical methods of pathology and baeteriology."

What effects drugs will have on the early treatment of tuberculosis remains speculative. As yet no observations are reported on their use in humans, but early reports will undoubtedly be published in the near future. Adams now has several children on ambulatory isoniazid treatment, and the first retesting with tuberculin will be done shortly. Some fear has been expressed about the toxicity of the effective drugs, but Adams has not eneountered any untoward effects. Even should the tubereulin reaetion reconvert to negative, this reaction must be evaluated with the knowledge that spontaneous reeonversion does seem to oeeur in a small per eent of persons and that, irrespeetive of the state of skin reactivity, the primary-type lesion does not redevelop in the untreated individual.[28]

Coneerning the effeetiveness of the various drugs used in elinieal tuberculosis, preliminary reports of the United States Publie Health Serviee Cooperative Investigation of antimierobial therapy of tuberculosis[29,30] show that isoniazid plus PAS are as effeetive as isoniazid plus streptomyein, and all 3 drugs used together. They eonelude that the use of isoniazid plus streptomyein or of all 3 drugs together should probably not be routinely employed in a therapeutic regime.

The ability of the tuberele bacillus to develop resistanee to the drugs presently used in the treatment of tuberculosis has been repeatedly mentioned as a potential danger not to be underestimated. The problem of infeetion with drug-resistant organisms in persons who have never been treated with the drugs is being reported with inereasing frequency, although still a rarity, and represents a public health hazard that must be reeognized.[31]

However, it is not probable that the program of early treatment diseussed in this paper would add to this problem.[5] Cohen [32] points out that the development of resistance takes time and that continuanee of a positive sputum after this time oeeurs in only about 20 per eent of all persons treated. These patients are almost invariably those with extensive canitary disease, older and far more advaneed lesions than would come under the limits of "early treatment." Treatment of recent converters who have had contaet with tubereulosis wards and hospitals, however, must be evaluated in the light of the knowledge that their infeetion may be caused by drug-resistant bacilli.

Myers[4] reflects the view of several authorities who would hold in reserve one of the more effective drugs, either streptomycin or isoniazid. With the recent evidence that such therapy is probably just as effective, this approach should offer sufficient protection to both the individual infected and future potential contacts in case of later active disease without compromising the potential beneficial effects of early treatment. The question of efficiency and practicability of utilization of the different drugs currently being used is still open to discussion and to future experience.

Having discussed several of the theoretic aspects of the early treatment of the recent converter, it becomes apparent that we have insufficient basic knowledge of the tubercle bacillus, the disease it causes, and the weapons with which we treat the disease to be able to predict *a priori* just what, if any, results will ensue from a given aspect of treatment. We are left with "hunches" and "impressions" as the ultimate foundation for our hopes and expectations at the present time. Careful and adequately controlled clinical studies, such as those being conducted by Adams and the United States Public Health Service, will help answer many questions regarding the effect of early treatment and also to understand the tuberculin reaction in a more meaningful manner.

A very real problem in instituting any effective program for the treatment of the recent converter rests in our ability to find him. Frequent tuberculin testing is the only means by which we can do this at present.

Quite aside from the possibility of an actual cure before manifest disease develops, or the abortion of relatively infrequent but nonetheless serious complications of primary tuberculosis, the use of the test as dictated by the needs of a program to discover the recent converter has real value in itself.

A recent survey of 2,421 kindergarten children in Kansas City schools, who were retested one year later when in the first grade, discovered 19 children who had developed a positive tuberculin reaction during that time, a rate of 0.8 per cent.[33] Follow-up studies of the contacts of these converters uncovered 15 cases of active tuberculosis for a yield of slightly less than 2 per cent. In an extensive tuberculin testing program in the schools of St. Louis, Missouri, using the patch test, the first report covering more than 15,000 tests applied to children showed that about 4 per cent reacted positively.[34] Follow-up studies of the positive reactions and contacts of these children with roentgen examination has uncovered 13 cases of active tuberculosis, 8 adults and 5 children. This represents a yield of nearly 2 per cent. In both these studies, the yield has been better than 10 times the national mobile x-ray figures and reflects the closer relationship in time with initial exposure to active disease, development of infection, and conversion of the tuberculin reaction. The mere knowledge of recent conversion offers greater protection to the individual because these persons are known and can be followed more closely during a period when the development of clinical tuberculosis is highest.

In a paper by Myers and associates[35] soon to be published, in which results of 28 years of tuberculin testing of Minneapolis parochial school children are analyzed, the figures for 1954 show that of the 11,976 student enrollment, of which 98.7 per cent were tested, the over-all incidence of reactors was 3.9 per cent with about 1 per cent reactors in kindergarten and progressing in a nearly linear fashion to slightly over 5 per cent at age 13. The results of the Kansas City survey previously mentioned, which showed a rate of conversion of kindergarten children of 0.8 per cent, is comparable to the Minneapolis survey. Both these surveys refer to metropolitan areas, and the rates are a good deal higher than in some rural areas. In Minnesota, it is known that there are large areas in which there is not a single positive reactor to tuberculin in sizable school populations. The opposite extreme of the incidence range of school children with positive reactions is reflected in recent figures from a survey of 21,648 New York City high school students, 1950-1952, which showed 12.8 per cent with positive reactions.[36] Infection of children with the tubercle bacillus is still occurring in a substantial proportion of the school population, a fact which makes the school system a likely place to institute frequent tuberculin testing.

Experience has shown that the routine application of the Mantoux skin test, or equivalent, is a feasible procedure for administration to large populations. Such frequent application of the test as is being used by Adams is probably not necessary, but how infrequently the test can be applied without seriously compromising possible effects of early treatment has yet to be determined. There are several programs for the routine testing of school children in the United States, but one of the oldest and most efficient of these is being administered in 4 counties of southwestern Minnesota, comprising an area of 3,800 square miles and a total school enrollment of nearly 15,000.[37] This program has been in effect since 1930 and has centered around the fa-

cilities of the Riverside Sanatorium, Granite Falls, under the direction of Lewis S. Jordan. A concerted and persistent effort has been made to get 100 per cent of all students and employees of the schools tuberculin tested every two years, all positive reactors being examined with a chest x-ray film and proper follow-up studies. Employees are required to comply with the program, but written consent must be obtained from the parents or guardians of the students before they can be included in the program. With the backing of civic and other local groups, this program has become an integral part of the community, a service that the people have come to expect and want. In 1943, a system of accrediting schools and awarding certificates for active cooperation was devised, introducing an element of interschool competition. The success of the program is gratifying indeed. Jordan[38] recently reported that a total of 175 schools have now been tested and the over-all percentage of the students participating is a bit over 95 per cent. Participation is 100 per cent in 108 schools and, of these schools, 79 per cent had not a single reactor. This is powerful evidence, indeed, for the value of the tuberculin test when properly used. Jordan prefers to use the intracutaneous skin test rather than the patch test, because he found that the children tended to play with the patch and, thereby, interfered with a proper intepretation of a reaction or lack of it. However, the school testing program now in operation in St. Louis, Missouri, is using the patch test exclusively with excellent results.

The accuracy of the patch tests available today is not good when compared with the intracutaneous method of tuberculin testing. Furcolow has found that available patch tests failed to give a positive reaction in nearly 30 per cent of all persons who reacted positively by the intracutaneous route.[39] He is presently working on a stronger patch with which he hopes to decrease this discrepancy. Another problem associated with the patch test is the number of atypical reactions, a problem similar to that attending the interpretation of high dose tuberculin intracutaneous tests. Either method, however, is relatively easy to employ and on a large scale can be done at a cost of between $.10 and $.15 per test, applied and read.

It is of particular importance that a conversion of the tuberculin reaction in infants and also in children of preschool age be recognized.[27] The great potential danger from tuberculous infection in this age group is well recognized. The physician should not overlook use of the tuberculin test in routine office visits or in well-baby clinics. The percentage of reactors in this group is much less, being about 1 per cent at 5 years of age in the Minneapolis survey and 4.3 per cent in 3,300 children in the New York study. It is regretful that many pediatricians, to say nothing of other practitioners caring for these infants and children, are not using the test to best advantage. Kendig[40] reports that a tabulation of 1,480 replies to a questionnaire sent to 2,500 practicing pediatricians showed that slightly over half, 55.5 per cent, used the tuberculin skin test routinely, but 21 per cent used it only after children were 3 years of age or older. Therefore, the test was not used in the very group in which the most benefits of protection could be offered if infection was known to have occurred. In addition to the danger from infection to these individuals, the fact should be pointed out that the efficiency of follow-up studies in uncovering cases of active tuberculosis among contacts of the reactor is higher. This reflects the fewer number of potential contacts of the young child.

The problem of the tuberculin converter in the so-called "high exposure risk" groups—nursing and medical personnel, the American Indian on reservations, certain ethnic groups, and family situations where exposure cannot be avoided—is of considerable interest because it appears that there is an alternative which is more applicable here than to the general population. Looking specifically at the problem in nursing and medical personnel, Myers and Waring both agree that "recent converters" should not be denied drug therapy if the individual wants it. In this group, the certainty of exposure and subsequent development of primary infection must be weighed against the chance that exposure or the development of primary infection is not a commonplace event. At the present stage of our understanding of drug therapy, it is perhaps too much to expect that a person should be subjected to repeated courses of drugs over the years just to obtain reconversion of a positive tuberculin reaction, if it occurs, and to keep the reaction negative. One may prefer to rely on the apparent immunity afforded by a positive tuberculin reaction, even though such immunity is not very adequate and completely unpredictable. If, on the other hand, infection is not so frequent, more benefit may be derived by attempted cure of an asymptomatic infection. Some data have recently become available that shed some light on the number of doctors who convert from a negative to a positive tuberculin reaction.[41] A follow-up of 2,683 graduates from the University of Minnesota medical school from

1930 to 1951, of which 98.8 per cent were traced, showed that there were 1,203 nonreactors at the time of graduation and 486 of these have subsequently developed a positive reaction, a rate of 40.4 per cent. The incidence of infection as indicated by the skin test has shown a decline since 1936 which is probably due to: (1) shorter period of observation, (2) decreased incidence of tuberculosis in the general population, and (3) to greater precautions taken to protect the physician both by himself and by the institutions in which he works.[42] Because of the increasing importance of preceding reasons 2 and 3, no basis exists for the oft expressed fatalistic attitude that medical personnel necessarily all convert.

The question of the efficiency of the immunity afforded by BCG—as a means of producing a positive reaction—is an intimate part of the problem. Palmer and Shaw[43] conclude that the available evidence is still too small to provide support for the effectiveness of BCG. Some data suggest that it may have a beneficial effect on mortality rates in Indian and Puerto Rican groups, but not on the morbidity rates.[44] In addition to the lack of uniformity of strains and the occasional serious reactions, including a few deaths, the principal objection to its use is the loss of the tuberculin reaction as a signal that infection with virulent bacilli has occurred.[45–48]

Until more data are available, each physician must follow his own convictions for the course he prefers to recommend to the persons in this segment of our population. As Waring[1] so poignantly stated, although in somewhat different context, we must decide to "either 'vaccinate and prevent' or 'tuberculin test and treat recent converters.'"

SUMMARY

1. General theoretic aspects concerning the early treatment of asymptomatic converters to the tuberculin sensitive state have been discussed.
   a. The tuberculin reaction is a reliable test that can be used to indicate infection at a stage when blood-borne substances can be expected to exert their effects efficiently.
   b. The relatively low incidence of complications, early and late, from primary tuberculosis is well established, although the complications can be very grave when they do occur. The importance of the primary lesions in reinfection type tuberculosis is controversial and is really an unknown quantity.
   c. The effects of antimicrobial therapy cannot be predicted *a priori* because of our poor understanding of the way in which they act. We know clinically, however, that early treatment of the symptomatic primary disease abates many complications, particularly the effect of isoniazid in preventing or inhibiting clinical meningitis.
   d. The potential public health hazard of developing drug-resistant strains of bacilli is probably real and must be recognized, but the ultimate threat resulting from the treatment of the recent converter does not appear very great.
2. Frequent tuberculin testing as dictated by the need of a program to find the recent converter has value in itself by resulting in a high-case yield in the follow-up studies of contacts of the recent converter.
3. The efficiency of routine tuberculin testing programs in the school systems suggests that these programs could be adapted to fit the requirements for the detection of the recent converter if developments should indicate value of early therapy.
4. The importance of following preschool age children with frequent tuberculin testing is stressed.
5. Whether it is advisable to apply the principles of early treatment of the recent converter in the so-called high-exposure group must be evaluated with the knowledge that (a) the immunity afforded by a positive reaction is unreliable, (b) the protective value of BCG is very questionable, and (c) the rate of development of tuberculin reactors in physicians is decreasing and can be expected to further decline in the years to come.
6. Perhaps the most important development which could be expected in the near future is the new role the general practicing physician will assume in the battle against tuberculosis. He would have the tools and responsibility not only for the diagnosis of tuberculosis, but for the largest part of the treatment as well.

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The condition of patients with pneumococcal pneumonia usually improves within forty-eight hours if Tetracyn is given orally every six hours in doses of 0.5 gm. Since toxicity of the drug is negligible, Anthony J. Palazzolo, M.D., and associates of Philadelphia General Hospital and the University of Pennsylvania, Philadelphia, advocate use of the antibiotic when the patient is sensitive to penicillin, the pathogen is unknown, or a gram-negative organism is believed to be the causative agent.

Anthony J. Palazzolo and associates: Antibiotics & Chemother. 10:1075-1081, 1954.

Two Decades of Tuberculin Testing

EDGAR S. KRUG, M.D., AND HERBERT R. GLENN, M.D.
University Park, Pennsylvania

FOR THE PAST several years, we have thought that the positive reactors to our tuberculin testing program for new students has become reduced, from the percentage standpoint, to a remarkable degree.

For this reason, we surveyed our records over the past twenty-two years. The results are shown graphically in figure 1.

EDGAR S. KRUG, *a 1929 graduate of Jefferson Medical College, is assistant university physician at the Pennsylvania State University, University Park, Pennsylvania.* HERBERT R. GLENN, *a 1927 graduate of Jefferson Medical College, is director of the university health service at the Pennsylvania State University, University Park, Pennsylvania.*

The material used in this work varied as follows:

1933 – Two-strength old tuberculin
1934-1948 – Two-strength PPD.
1949-1954 – First-strength PPD. x 5
1946 – no entering class to examine

The figures as represented in the graphs were the results obtained by testing 30,267 males and 11,788 females or a grand total of 42,055 individuals tested during the twenty-two-year period.

Attention is drawn to the fact that except for the years 1943 and 1944, when the number of females exceeded the males, and in 1949 when their numbers were almost equal, the proportion noted in the total figures was maintained.

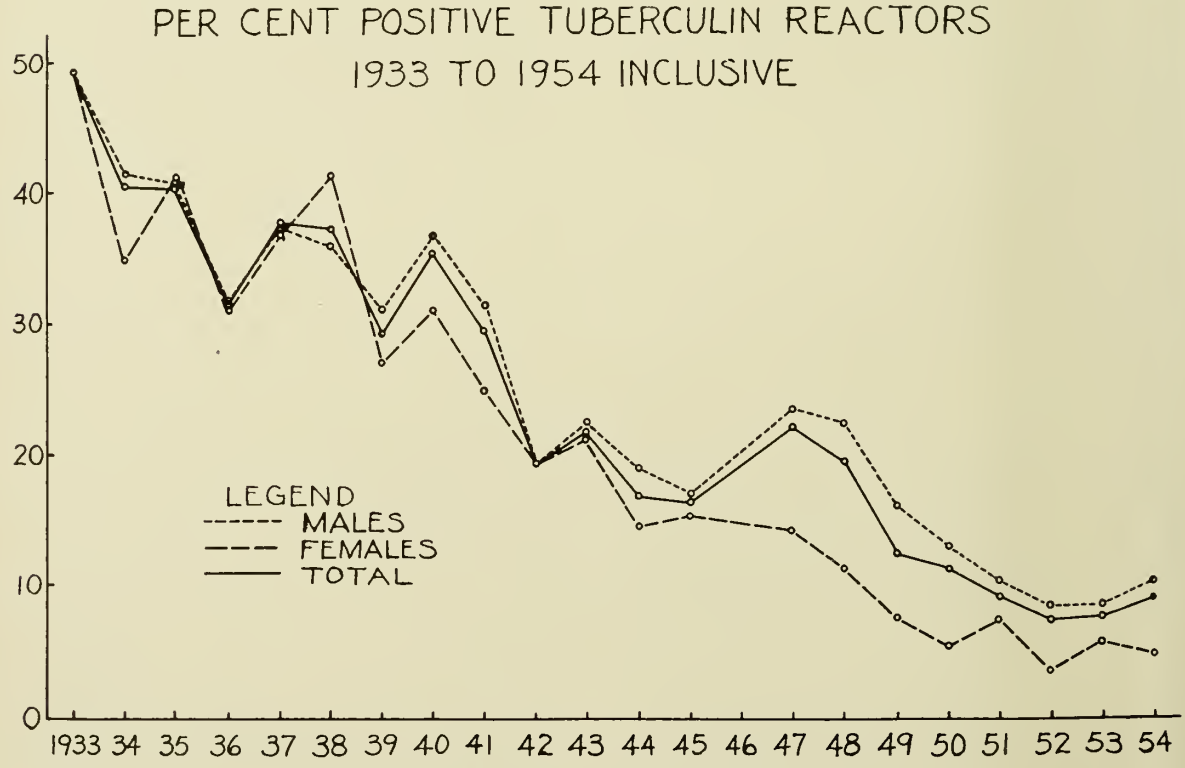

Fig. 1. Results of the twenty-two year survey.

Diagnosis of Chest Diseases

The Roentgenologist's Approach

SEWELL S. GORDON, M.D.

Minneapolis, Minnesota

An attempt will be made to outline the thought processes of an individual roentgenologist as he goes about the interpretation of chest roentgenograms. The general technic of interpretation will be discussed and a few of the individual problems taken up, so that the general pattern of roentgenologic diagnosis, as applied to chest disease, can be presented.

Such a discussion, it is hoped, may serve several useful purposes. Primarily, it should help the referring physician to evaluate the report he receives from the roentgenologist. He should understand how much significance the roentgenologist attaches to the various findings he describes in his report. Some findings of minor significance are often mentioned by the roentgenologist for the sake of completeness and objectivity; yet these can be dismissed without further investigation. On the other hand, he may mention certain equivocal findings which, while not of a definite nature, do demand additional investigation. The clinician should understand the difference between these 2 types of findings and then evaluate them for the patient.

Secondly, the clinician may gain a more sympathetic understanding of the problems facing the roentgenologist and the methods he uses in handling these problems. In this regard, the importance of obtaining from the referring physician the patient's history, pertinent physical findings, and laboratory data should be emphasized. The physician should, for example, see that the roentgenologist makes a special search for certain findings when the patient has a history of sudden onset of chest pain. A thorough scrutiny of the ribs may lead to the detection of a fracture without displacement, or possibly a small osteolytic lesion of myeloma. In the younger age group, a minimum change suggestive of pneumothorax might be detected. In this situation, he would be apt to order an examination of the chest in expiration where the diagnosis becomes obvious. Recently I had occasion to review a case in which a pulmonary lesion was not detected on a photofluorogram nor on a subsequent 14 x 17 in. roentgenogram. The latter study was ordered because the clinician suspected the possibility of carcinoma of the lung, but at no time was the radiologist informed about the cough and left chest pain suffered by the patient (figure 1). Both roentgenograms were considered routine, particularly since the patient had been admitted to the hospital for an unrelated disease. In reviewing the patient's roentgenograms, slight prominence of the left hilum was quite apparent, and also a minimum elevation of the left leaf of the diaphragm. The findings were not at all striking, but attention would have been directed to them if the roentgenologist had known about the patient's symptoms.

Having the clinical data available is useful in the detection of abnormality as described previously, but it is even more useful in the presence of a definite abnormality, in which case a more intelligent analysis of the positive findings can be made. As an example, we may be dealing with a disseminated nodular infiltration which is bilateral and symmetrical. A multitude of disease processes may have such a roentgenographic appearance (figure 2). On interrogation of the patient we learn that he is completely asymptomatic; he has known that he had a pulmonary infiltration for over five years; and that he has done sand blasting in a foundry for twelve years. This history, of course, suggests the possibility of silicosis. The roentgenogram is entirely consistent with silicosis. Thus, a definite diagnosis has been established. In the absence of a simple history, only a vague roentgenologic report could have been rendered.

The third purpose of this discussion is to attempt to define a healthy attitude on the part of the clinician concerning the report he receives from the roentgenologist. In general, his attitude should be one of constructive skepticism.

SEWELL S. GORDON, *a 1943 graduate of the University of Minnesota Medical School, is with the department of radiology at the University of Minnesota and Veterans Administration Hospital, Minneapolis.*

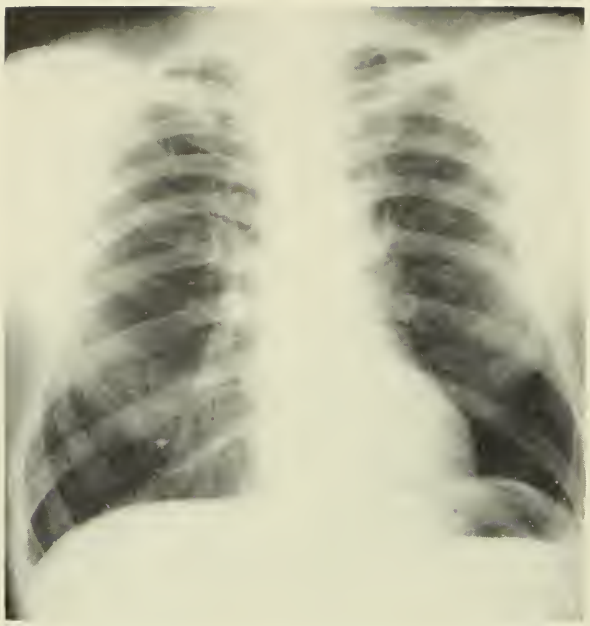

Fig. 1. Note faint prominence of the superior aspect of the left hilum and slight elevation of the left leaf of the diaphragm. Findings were due to a carcinoma involving the superior segment of the left lower lobe.

He must not believe without questioning. He should remember that few occasions arise when a roentgenologist confronted with a problem in chest diagnosis can be absolutely specific. Usually his conclusions are based on the relative probabilities of certain shadows of varying densities and configurations representing certain disease entities. If, therefore, his conclusions and differential diagnosis do not agree with the clinical data, further clinical and laboratory investigations should be carried out to prove or disprove his impressions. On the other hand, it is not prudent to dismiss his suggestions because they do not agree with the apparent clinical situation. The experienced clinician recognizes the frequency with which unsuspected shadows reveal themselves on the roentgenogram in spite of an absence of signs or symptoms of chest disease. On occasion, certain characteristic appearances allow the roentgenologist to suggest a specific diagnosis with a fairly high degree of accuracy. This type of report should not be dismissed lightly.

The relative probabilities of the various diagnostic considerations in any given case are difficult for the roentgenologist to put in words. To do this would require a report in which each diagnosis would be followed by a percentage figure. It is far better for the clinician and roentgenologist to discuss the case at hand. In this way each gives to the other the full benefit of his special knowledge of the case. Together they arrive at more sound conclusions than either could achieve by himself. In large institutions where the roentgenologist is often not immediately available for consultation, one of the best ways of carrying out such clinical-roentgenologic meetings of the mind is at a special conference held, perhaps, once a week.

This attempt to set down a single method of analyzing chest roentgenograms must be recognized as the product of one individual's background and experience. No two radiologists have had an identical training and experience. We do not expect them, therefore, to have an identical approach. However, most men in the field run into similar diagnostic problems and try to resolve them in the same general way and by the best means available. Their individual technics and types of examinations vary, but, by and large, they tend to arrive at the same ultimate point in their diagnostic work-up. Beyond this point they cannot go without the help of their colleagues.

ANALYSIS OF ROENTGENOGRAMS WITH QUESTIONABLE ABNORMALITIES

The roentgenologist frequently detects a questionable lesion or a variation from the normal, the exact significance of which is doubtful. He may feel that additional studies will help to determine whether or not an abnormality is present, and, if so, whether or not it is significant. Past experience has proved that a minority of such findings upon further investigation yield

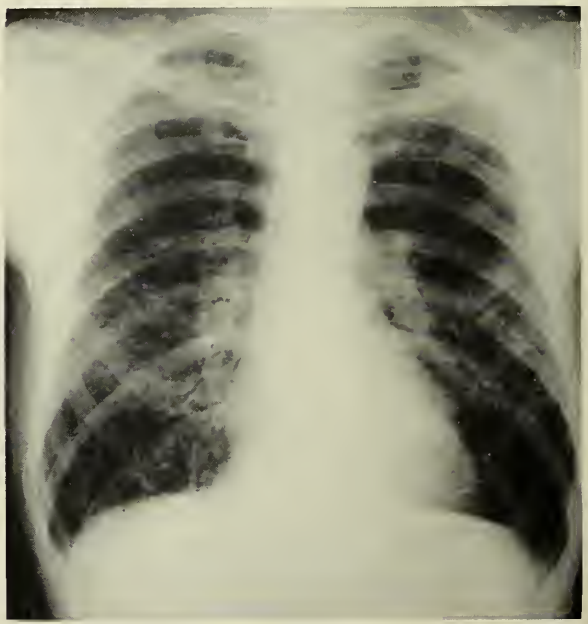

Fig. 2. Disseminated nodular infiltration, bilaterally symmetrical which could be due to a host of disease processes. History of exposure to silica dust established diagnosis of silicosis.

positive pathologic lesions, and, furthermore, that only a minority of these lesions require medical or surgical management. Yet this is the group of cases called back for investigation of minor aberrations from which we obtain the highest yield of early lesions amenable to good medical or surgical management.

The roentgenologist may suggest that a questionable enlargement of the left hilar shadow is present and request fluoroscopy. At fluoroscopy the left hilar enlargement is again demonstrated, and also slight enlargement of the right hilum may be apparent. The impression is gained that the prominent shadow follows the contour usually assumed by the pulmonary artery. Roentgenograms are made in inspiration and expiration, as well as in the lateral projection. The lateral confirms the impression of an enlarged hilum, but no evidence of localized obstructive emphysema is noted on the roentgenograms or at fluoroscopy. Usually at this point the roentgenologist feels confident that the hilar enlargement has been adequately explained on the basis of moderate generalized pulmonary emphysema, with secondary pulmonary hypertension. Occasionally, however, he feels that planigraphy is indicated to more definitely exclude a neoplasm. Perhaps planigraphy may demonstrate some scattered calcification in hilar lymph nodes, not detectable as such on the plain roentgenogram. With this finding, the enlarged hilum has been explained. From the patient's point of view, however, the expense has been considerable in addition to some loss of time from work, with nothing tangible resulting from the roentgenologic investigations. At this time the clinician plays a very important role in explaining to the patient that the roentgenologic diagnostic work-up was important, and that the patient should be pleased to know that the abnormal findings in his chest are on a benign basis. In the back of his mind the experienced clinician realizes that the results might have been different, requiring a thoracotomy for carcinoma of the lung, or possibly a malignant thymoma.

Most often the questionable infiltration that the radiologist reports turns out to be a local exaggeration of vascular markings. These may or may not be associated with recognizable emphysematous blebs, which often cause local compression of lung, and, therefore, approximation of the normal vascular structures. These questionable infiltrations are much more common in obese individuals, who are unable to take in a very deep breath on the one hand, and who have a reduced ratio of lung-tissue thickness to chest-wall thickness on the other, making it technically difficult to avoid local exaggerations of vascular markings. Commonly, these findings are localized to the apices or subclavicular areas. The roentgenologist may order stereoscopic or apical lordotic projections, or both. The former not only allows visualization in three dimensions, facilitating an "uncoiling" of the individual vessels entering into a local exaggerated pattern, but also allows observation of the questionable lesion from two different angles, in one of which overlapping blood vessels are usually quite apparent. The same technic is used to determine whether a nodular shadow is within a lung or a rib. For example, a benign bone island stays with the rib in both roentgenograms.

The apical lordotic projection has the virtue of eliminating, to a large extent, the factor of overlying ribs and clavicle. This elimination is accomplished by attempting to superimpose the anterior and posterior segments of each individual rib in a horizontal plane, which gives an unobscured view of the lung substance between the ribs. This examination is useful also in bringing out more prominently an obscure shadow in the superior mediastinum or the adjacent lung tissue. This area is commonly obscured, particularly in the kyphotic individual, by the telescoping of posterior ribs and thoracic vertebrae.

If these additional views substantiate the presence of an infiltration, further clinical studies must be done and possibly further roentgenographic examinations are indicated.

A multitude of other findings may necessitate calling a patient back for further roentgenologic study in order to elucidate such findings. For example, the postero-anterior roentgenogram may show a questionable retrocardiac density. An examination with overpenetration, or with Bucky technic, and a lateral projection corresponding to the side involved often resolves the question of whether or not an abnormality is present. Further investigation, if a lesion is present, depends somewhat on its appearance and location. If the lesion is an isolated nodular shadow, it is worked up from that point of view. If it is a triangular paravertebral shadow, it probably represents an atelectatic lobe or abnormal pleural density and requires additional studies to delineate the bronchi and evaluate the spine. If the retrocardiac shadow is round and located in the costovertebral angle in close relationship with the diaphragm, the roentgenologist may suggest an examination of the stomach with barium, having in mind the strong likelihood that a hiatus hernia is present.

A prominent shadow in the right cardiophrenic angle may, at fluoroscopy or on further roent-

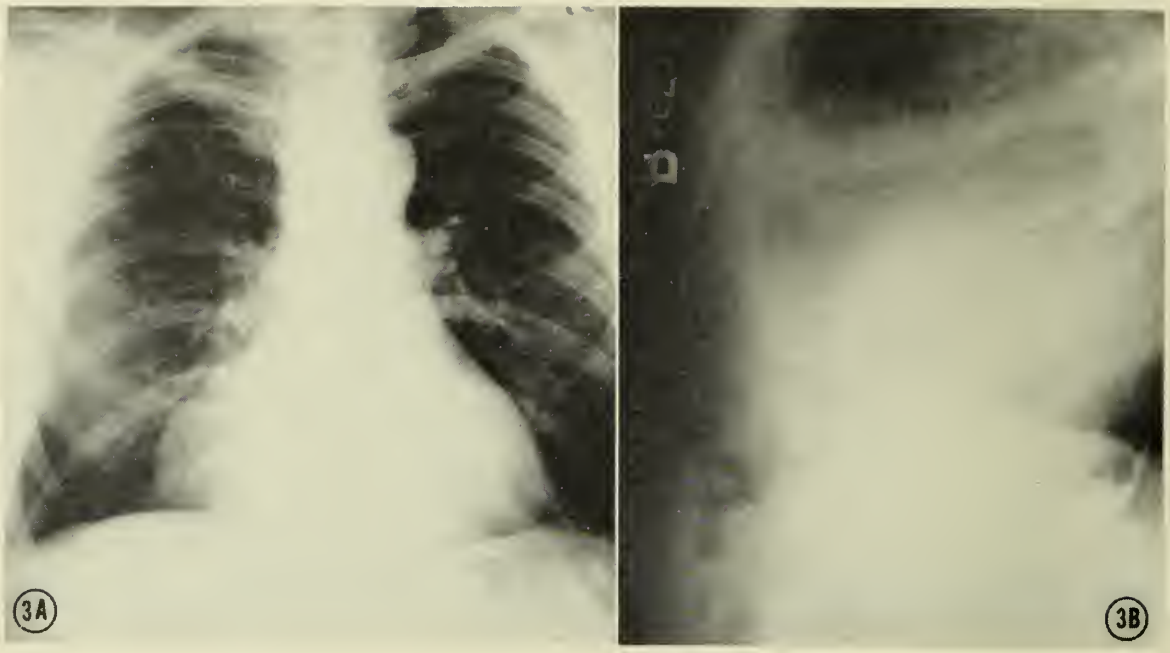

Fig. 3*a*. Large mass density in right cardiophrenic angle does not obscure the heart border, but adds to density of the right side of the heart. (*b*). Lateral projection shows a mass density interposed between sternum and anterior margin of the heart. Note also the high position of the gas-containing colon. Diagnosis of herniation of omentum through the foramen of Morgagni was suggested. This was confirmed at surgery.

genographic analysis, turn out to be a localized eventration of the diaphragm or a prominent epicardial fat-pad, which obscures the lower right heart border. Barium enema may be requested to evaluate the possibility of a hernia through the right parasternal hiatus (Morgagni) (figure 3).

PROCEDURE USED FOR A RECOGNIZED CHEST ABNORMALITY

At this stage in the analysis of the chest roentgenogram, it is assumed that all of the artefacts have been ruled out and the anatomic variations and other findings of little significance have been excluded. The problem now concerns an abnormal shadow somewhere in the chest. Attempts must be made to localize it in one of the anatomic elements of the thorax; namely, the extrapleural space, the pleura, the bony thorax — including sternum, ribs and spine — the diaphragm, the mediastinum, or the lung parenchyma. In addition, it may at times be difficult to determine whether the disease process is primarily intrathoracic, or whether it encroaches upon the chest from the neck above or the abdomen below (figure 4).

The problem of anatomic localization is important and must be resolved before an intelligent analysis of the roentgen findings can be made. A detailed discussion along this line is beyond the scope of this paper. However, a discussion of the approach to such a problem seems worthwhile.

Given a hypothetic case of considerable increased density in one side of the thorax, attempt is made to answer a series of questions that help localize the density anatomically.

Are radiolucent stripes corresponding to bronchi seen coursing through the density? If so, the density is in the lung.

Does the density follow the pattern of localization of a free pleural effusion? Does it move to the dependent portion of the thorax on change of position? Does it have a scalloped edge along the margin, including mediastinal, of the pleura? If so, loculation of fluid comes to mind rather than free fluid. Does the density have a lobar distribution or is the distribution peripheral like fluid?

Are the ribs intact? If a fracture is seen, there may be a collection of blood in an extrapleural pocket or within the pleura itself. In the latter situation, there is often an associated fluid level due to the presence of pneumothorax.

Is the affected hemithorax expanded or contracted? The contracted hemithorax shows approximation of ribs, elevation of the corresponding leaf of the diaphragm, and deviation of mediastinal structures toward it. This is most frequently due to atelectasis, but can also be due to pronounced pleural thickening or to unilateral fibrosis. The expanded hemithorax is recog-

nized by displacement of the heart and mediastinal structures away from the side of homogeneous opacification, spreading of the ribs on the affected side, and depression of the corresponding leaf of the diaphragm. If the hemithorax is expanded, the first thought is of massive pleural effusion, but massive neoplasm or massive cardiac enlargement must also be taken into consideration.

After the anatomic localization of the disease process has been clarified, and this may be obvious on the initial roentgenogram, we proceed with the analysis of the positive findings. Unless there is clinical or roentgen evidence to the contrary, the shadow that is seen is assumed to be due to an acute process. Thus, if an infiltration that looks like pneumonia is seen, it is called pneumonia. Often the radiologist does not mention the possibility of some underlying, more chronic process, but such a process should not be assumed to be nonexistant. Even if the patient responds dramatically to his therapy, it is important to x-ray the chest until completely clear.

At this point, having discussed largely the generalizations concerning the diagnosis of chest disease, a few of the many specific problems encountered on a chest service should be covered.

INCOMPLETELY RESOLVED PNEUMONIA

Let us assume now that the pneumonia has shown only partial resolution after a period of six weeks. At this time, the etiology of the poor resolution must be determined.

A large number of chronic pulmonary diseases may masquerade as an unresolved pneumonia, so an attempt to make an etiologic diagnosis is important. Occasionally poor resolution is due to underlying diseased pulmonary parenchyma as seen with emphysema or fibrosis. At other times, it is due to infection with an unusually virulent organism such as is seen with Friedländer's bacillus, a Staphylococcus, or an occasional pneumococcus. Finally, it may be due to diseased or obstructed bronchi. Bronchial obstruction may be due to retained secretions, possibly a foreign body, and most significantly by tumor. By diseased bronchi we mean primarily bronchiectasis.

The importance of having any and all previous roentgenograms of the chest for comparison cannot be overemphasized. This fact can be well illustrated by an example. On a busy chest serv-

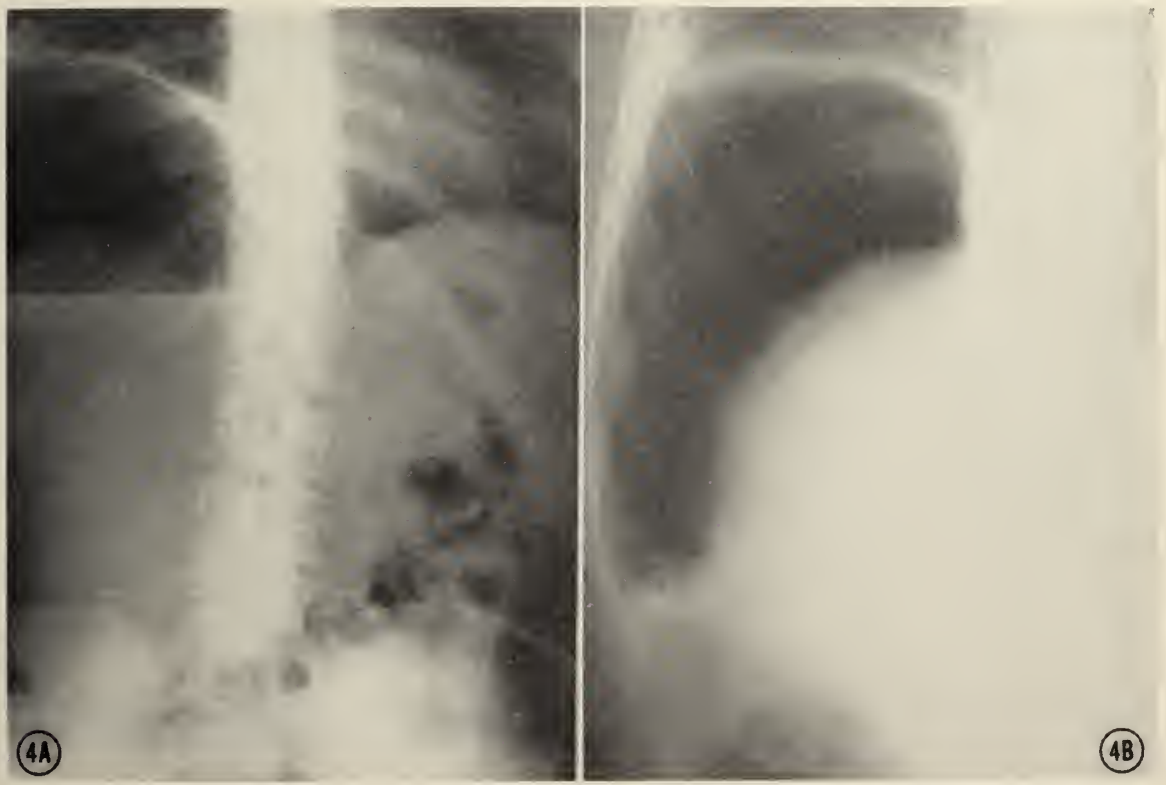

Fig. 4*a*. In the upright abdomen, difficulty in distinguishing pneumothorax and pneumoperitoneum is obvious. (*b*). In the lateral decubitus projection, diagnosis of pneumothorax was established by virtue of demonstration of the slips of origin of the diaphragm from the chest wall, as well as confinement of fluid at the midline.

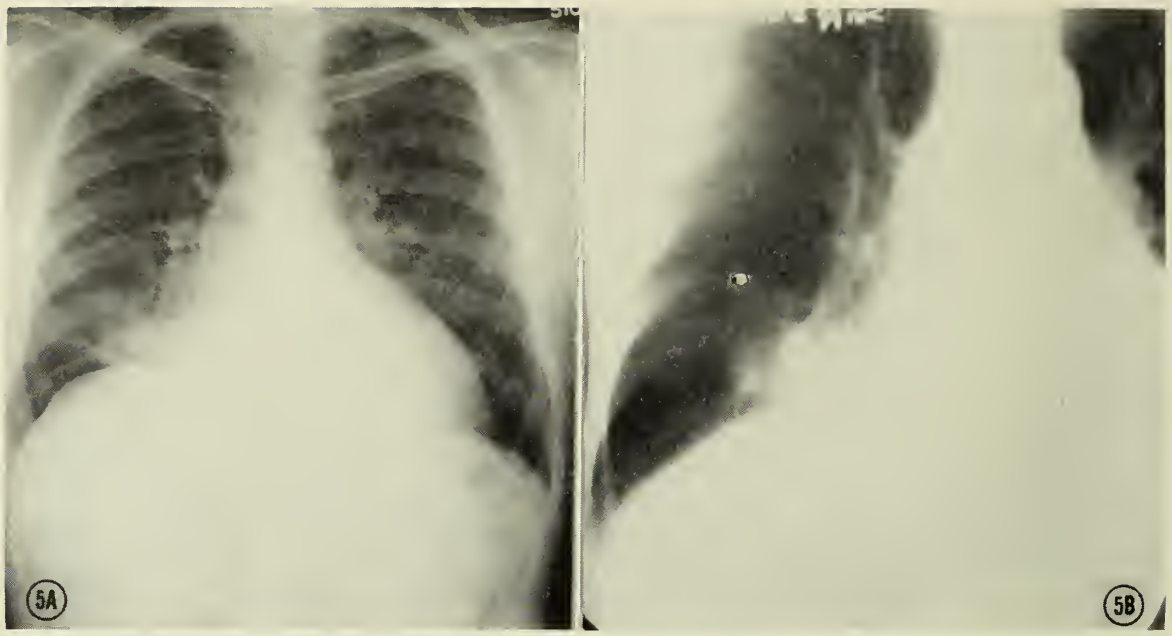

Fig. 5*a*. Postero-anterior projection demonstrates an ill-defined density in right lower lung field medially. Note deviation of trachea to the right, and elevated right leaf of the diaphragm. These findings indicate considerable collapse in the lower lobe. (*b*). Planigraphy established patency of right lower lobe bronchus. These findings were considered suggestive of lipoid pneumonia.

ice, an asymptomatic localized lipoid pneumonia is often encountered, which, on a single hospital admission, with one roentgenologic work-up can not be distinguished from carcinoma of the lung. However, when old studies are compared with the more recent ones, it is recognized that only a very slow progression has occurred, which can be measured in terms of years rather than months. With this evidence at hand the roentgenologist may suggest the diagnosis of lipoid pneumonia. If then, a history can be elicited from the patient of long-time ingestion of mineral oil for constipation, along with any signs or symptoms of bulbar palsy, a tentative diagnosis can be made. Negative bronchoscopy and positive identification of oil in the sputum should support the diagnosis. If this evidence indicates a diagnosis of lipoid pneumonia, then a thoracotomy is not indicated, especially in the poor-risk type of patient in whom lipoid pneumonia is particularly common (figure 5).

The next step in the roentgenologic evaluation generally is planigraphy, which can be done with the patient in the frontal, lateral, or oblique position. Primarily attempt is made to evaluate the condition of the bronchi. We try to find any evidence of bronchial obstruction or other abnormality. If bronchial obstruction is met, we try to determine its nature. Occasionally evidence of dilated bronchi may be seen surrounded by rather homogeneous consolidation, which suggests the presence of bronchiectasis or possibly an organizing pneumonia. After evaluation of the bronchi, the lung parenchyma is evaluated. The planigrams often demonstrate cavitation or emphysematous bullae much more clearly than conventional roentgenograms.

Bronchography is the next step in the roentgenologic work-up. It is important that this study should not precede planigraphy unless water-soluble contrast medium is being used. Otherwise, retained oily medium obscures detail and thus makes evaluation more difficult. Bronchography is a detailed technical procedure which should not be done haphazardly or as an afterthought by the bronchoscopist. The procedure is best accomplished by the otolaryngologist working hand in hand with the roentgenologist. This study requires good local anesthesia, followed by aspiration of secretions from the tracheobronchial tree, before beginning the instillation of contrast medium under fluoroscopic control. At some centers this study is done without fluoroscopy, but it is doubtful if this technic is as satisfactory, particularly in the presence of a distorted bronchial pattern. If bronchiectasis is detected, a complete bilateral lung mapping, including all lobes and each individual segment, is necessary before surgery can be advised.

PROCEDURE USED WITH ISOLATED NODULE

A considerable volume of material has now been published considering the isolated nodule. The original concept of a round, homogeneous soli-

tary density of small size has been broadened to include a multitude of apparently solitary densities. This probably has evolved because of the difficulty in determining definitely whether a given density in the lung meets the earlier criteria. Detailed planigraphy should be carried out in all suspected solitary nodular lesions. In addition to the help this procedure gives in localization — small nodules frequently are not demonstrable in the lateral projection — often additional diagnostic information is obtained.

Bronchography is seldom of value in the isolated peripheral nodule. If, clinically, there is reason to suspect that the nodule might be metastatic to the lung, a roentgenologic cancer detection study of the urinary and gastrointestinal tracts should be carried out.

PROCEDURE USED WHEN A MEDIASTINAL MASS DENSITY IS PRESENT

The variety of pathologic entities which may be encountered in the mediastinum is so great that a detailed discussion of the various factors considered in arriving at a probable diagnosis cannot be carried out here. However, a list of questions about the lesion which need answering before a roentgenologist should venture an opinion are helpful.

1. What is the location of the lesion? This is the most significant question of all, because by knowing which lesions occur by predilection in each anatomic division of the mediastinum, the lesion can be put in a broad diagnostic pigeonhole. A frontal and lateral roentgenogram generally suffices for this localization. However, if the mass is in the apex, the lordotic projection can be used for antero-posterior localization by determining whether the mass stays with the posterior or anterior ribs. The lateral projection is very seldom helpful in demonstrating a small apical mass.

2. Is there evidence of bone erosion or pressure deformity? Only a few of the mediastinal lesions erode bone, and each has a characteristic site of erosion. In addition, different masses produce different types of erosion and pressure deformities. This finding is not a common one, but, when present, is quite helful. It is important to recognize that occasionally a bone tumor, primary in the thoracic cage and lying in the midline anteriorly or posteriorly, may encroach on the mediastinum and be difficult to differentiate from a primary mediastinal mass. Recognition of bone erosion, when present, is quite helpful in this situation. If the tumor originates in the costal cartilages, bone erosion would be a late manifestation.

3. Is there evidence of calcification? Certain tumors tend to calcify more often than others, and the type of calcification usually gives a lead in the differential diagnosis.

4. What is the relationship of the mass to the surrounding structures? Fluoroscopy and roentgenograms in multiple projections should be used in an attempt to "separate" the mass from the various overlying structures.

We look for evidence of pleural reflection over the mass. The finding of reflected pleura at both ends of a mass indicates an extrapleural localization.

5. Is there evidence of differential density within the mass itself or between the mass and the surrounding soft-tissue structures? Is there evidence of a gas-fluid level? If a gas-fluid level is present, the structure is probably related to the gastrointestinal tract, whether it be hernia, cardiospasm, or a duplication. Very rarely a bronchogenic cyst or dermoid may contain an air-fluid level after emptying into a bronchus.

If the mass is more radiolucent than would be expected for a mass of this volume, the possibility of a lipoma is suggested or, rarely, a dermoid. However, this finding is often deceptive in the thorax, since the mediastinal mass is generally surrounded by an air-containing lung, whereas the organ of reference — often the heart — is not only thicker in the dimension of reference but also is overlaid by other structures of normal soft-tissue density.

Another finding which we look for, but rarely see, is an oil-fluid level. This level is an occasional finding in a mediastinal dermoid, and is caused by the presence of floating sebaceous material on top of the aqueous content of the cyst.

6. Is there evidence that the mass extends beyond the chest? If the mass extends into the neck, a hygroma comes to mind in children, or a substernal thyroid in adults. If it extends below the diaphragm, special studies may be necessary to demonstrate it. An overpenetrated projection of the chest often shows the dilated esophagus of cardiospasm as an abnormal soft-tissue mass crossing to the left behind the heart and extending to the diaphragm below the level of the heart.

7. What is the shape and definition of the mass? If it is a smoothly-rounded oval, a cyst is the first thought. If there is evidence of polylobulation, matted lymph nodes are considered. If the mass blends with the surrounding structures along one or more margins, lipoma comes to mind.

8. What is the relationship of the mass to the

esophagus, trachea, or bronchi? Unless it can be clearly determined that the mass is separate from the esophagus, trachea, or bronchi, the corresponding esophagram, bronchogram, or both should be carried out.

9. What are the characteristics of the mass at fluoroscopy? If there is evidence of expansile pulsation, an aneurysm is strongly suspected or more rarely an arteriovenous fistula. Expansile and transmitted pulsations are often difficult to distinguish. The finding of expansile pulsation is difficult to evaluate and is unreliable if not well defined. Kymography may be useful in substantiating a fluoroscopic impression. This technic is a method of recording on a roentgen film the pulsations of any moving density recognized fluoroscopically.

If the mass does change configuration with respiration or change in position, cysts are thought of more often than solid tumors, since they tend to be more "fluid."

10. Do serial films show evidence of growth in a mass, or has the mass been relatively stationary for years? Generally a series of chest roentgenograms dating back many years are not available. Some of the mediastinal neoplasms have characteristic growth patterns that can be used as additional data in the differential diagnosis.

Even with a complete diagnostic work-up of these mediastinal masses, it is still true, unfortunately, that a specific histologic diagnosis cannot be made in over 50 per cent of the cases. However, in the distinction between neoplastic and nonneoplastic mediastinal mass densities, the roentgen diagnosis fares much better. Since mediastinal neoplasms are all considered to be surgical problems, the importance of distinguishing the nonneoplastic mass densities, such as aneurysms, enlarged lymph nodes, hernias, and so forth, is readily apparent.

SUMMARY

An attempt has been made to follow the reasoning processes a roentgenologist uses in his interpretation of abnormal chest roentgenograms. Several specific categories of chest abnormalities have been discussed in an effort to describe the way in which the roentgenologist handles the individual problem. The mutual assistance that the referring physician and roentgenologist can offer each other has been stressed.

When diagnosing some types of mediastinal widening, venous aneurysms of the mediastinum, which are demonstrable roentgenographically, should be considered. In 2 patients with varicosities of the superior vena cava, Ted F. Leigh, M.D., and associates of Emory University, Ga., found that anomalous pulmonary drainage existed. Dilation of the hemiazygos and azygos veins in 2 other persons probably was the result of atheromatous changes in these vessels and portal and pulmonary abnormaliteis.

Ted F. Leigh and associates: Radiology 63:696-705, 1954.

Bronchogenic Carcinoma in Young People

JACOB SHORT, M.D., AND JOHN F. BRIGGS, M.D.
Minneapolis, Minnesota

Although bronchogenic carcinoma is a disease which occurs primarily during the later years of life, we are now recognizing that it may occur in the younger age groups. Occasionally this disease has been reported in children. Little emphasis, however, has been placed on the fact that it is becoming more common in the younger age groups. The signs and symptoms of bronchogenic carcinoma are not specific, and this condition can and does mimic any other intrathoracic disease. Failure to recognize the increasing occurrence of this disease in the younger age groups has led to many diagnostic errors. The diagnosis of bronchogenic carcinoma at any age, but more particularly in the younger groups, is best made by a high index of suspicion concerning the existence of the disease in any patient found to have a pulmonary lesion. During the last year, 3 cases of proved bronchogenic carcinoma have been seen in patients in their early 20's. The following case is reported in detail. The patient was a young 21-year-old woman. She consulted a physician on July 19, 1954 because of a severe hacking cough. She related that this cough began six months before. At the time she thought she had a cold. The cough persisted over the ensuing six months and approximately one month before seeing her physician, it became worse. The cough by this time was associated with shortness of breath on exertion.

Past history was irrelevant. She stated she smoked heavily and her relatives emphasized that at times she smoked as many as 3 packages of cigarettes daily. The length of time she had been smoking is unknown, but it was felt that perhaps she started smoking about the age of 16 years.

Family history was noncontributory. The examination at the time of admission to the hospital revealed a normal appearing white female who was not acutely ill but who coughed almost constantly. The entire physical examination was normal except for the chest. The blood pressure was 110/80, the pulse 120 and regular, and the temperature was normal. The heart sounds were distant, but the tones were normal and no murmur could be heard. Examination of the chest revealed the presence of bilateral pleural effusion. In addiiton, many moist and bubbling rales could be heard throughout both lung fields.

The laboratory examination was as follows: The hemoglobin was 11.6 gm. and the red count 4,120,000; the differential blood count was normal. An electrocardiogram revealed a sinus tachycardia with low voltage throughout the record. The x-ray film of the chest showed extensive bilateral pleural effusion which was most pronounced on the left side. In addition, dense infiltrates extended out from both hilar regions into the surrounding lung fields. Because of these densities and pleural effusion, the position of the heart borders was difficult to note accurately. The clinical impression was massive left pleural effusion with possible pericardial effusion. It was suggested that the condition could be the result of either rheumatic heart disease, tuberculosis, or bronchogenic carcinoma. On July 21, thoracentesis was performed and 1,000 cc. of clear-colored fluid was removed from the left pleural cavity. Examination of this fluid was negative. No evidence of tuberculosis was noted and no malignant cells were seen. The pathologist reported the presence of cells in the pleural sediment which he considered to be of inflammatory origin. Repeated sputum examinations were negative for organisms. The tuberculin test was negative. An x-ray film examination of the chest after thoracentesis showed decrease in the amount of pleural effusion in the left chest, and the lung fields revealed pronounced congestive changes. Her course in the hospital was afebrile, but shortly after thoracentesis her condition worsened. She became acutely ill, the heart rate increased, distention of the veins in the neck was visible,

JACOB SHORT, *a 1928 graduate of the University of Minnesota Medical School, specializes in internal medicine in St. Paul.* JOHN F. BRIGGS, *a 1929 graduate of the University of Minnesota Medical School, is associate professor of clinical medicine at the University of Minnesota.*

and dyspnea became pronounced. Pleural effusion increased in the left chest and also in the right chest, and she became cyanotic. On July 28, the cyanosis became pronounced and dyspnea more severe. On July 29, while being examined, she died suddenly and a tentative diagnosis of terminal pulmonary embolism with pulmonary infarction was suggested. The presence of congestion in the lungs with obviously increased venous pressure, small peripheral pulse, and a silent heart suggested also that constrictive pericarditis or myocardial involvement was present. The discussion of the necropsy will be limited to the findings in the chest. Bilateral pleural effusion was present. Both lungs were studded with tumor tissue, and the pleura overlying the left lower lobe of the lung was covered with carcinomatous metastasis. A pulmonary embolism with infarction of the right lower lobe of the lung was also present, and there was carcinomatous involvement of the pericardium. Microscopic examination revealed the tumor to be an alveolar cell carcinoma.

SUMMARY

A case is presented of a young white woman whose presenting complaints were cough and dyspnea. The findings of bilateral hydrothorax were confirmed by the x-ray film examination. The pleural fluid was considered negative at the initial examination. In addition to the apparent involvement of the pleural spaces and the lungs, evidence of congestive heart failure was present. The patient's condition deteriorated rapidly and death followed a pulmonary embolism. At necropsy the malignant nature of the lesion was established. When the original pleural fluid sediment was reviewed after autopsy, the pathologist stated that the cells were malignant and not inflammatory. It is interesting to note his comment on initial examination of the sediment that these cells were believed to be malignant, but, in view of the patient's youth, this impression was discarded in favor of inflammatory cell reaction. Microscopic examination of the pericardium revealed that tumor tissue was present in the pericardium.

THE OCCURRENCE of pulmonary hyaline membranes is almost twice as frequent among infants of diabetic mothers as among other newborn babies dying during the first few days of life. W. D. Winter, Jr., M.D., and Sydney S. Gellis, M.D., of Boston made microscopic sections of the lungs of 40 infants who died between the ages of 1 hour and 14 days. Significant hyaline membrane formation was found in 21 of 27 infants whose deaths were not attributable to major anatomic causes but in only 3 of 13 infants in whom the reason for death could be determined. Although cesarean section apparently increases the incidence of the anomaly, the high fetal mortality rate justifies the operation for diabetic women. No relation has been found between membranous formation and congestive heart failure in the child.

W. D. WINTER, JR., and SYDNEY S. GELLIS: Am. J. Dis. Child. 87:702-706, 1954.

Progress Report of Socialized Medicine in Great Britain

JAMES ROGERS FOX, M.D.
Minneapolis, Minnesota

In 1952 I was fortunate to be in the position of practicing medicine in Great Britain under the panel system, a report of which was made in JOURNAL-LANCET. This experience gave me the opportunity to learn the hidden and often serious problems to look for in terms of care of the patient, standards of practice, encroachment upon freedom, and preparation for the future as in training and research. With this background and with numerous relationships established, I returned in 1954 to Great Britain where a progress report was undertaken.

My general approach was to interview the following groups: (1) organized medicine in the form of the medical association, (2) government medicine where I talked with the director of the program and his subordinates, (3) the practicing general physician in both urban and rural areas, (4) the specialist in both the hospital and in private practice, (5) the medical student and graduate student, (6) the beginning practitioner, (7) the patient, and finally (8) the press. I had the feeling that each group had an "axe to grind" and only by talking to them could I get a relatively true picture without again actually participating in the practice.

To delve into the background a bit, I believe it must be remembered that historically the United States began as a democracy, whereas Great Britain has evolved from the feudal system which, as a result, has required different measures to arrive at the state of democracy.

Tradition plays an extremely important role also, and one which is difficult for us to understand in light of the fact that a change from tradition could produce more efficiency in many instances. The population and size of the country together with communications, transportation, and finance also point out the fact that in *no* way can any program be compared nor suggested for the United States. Whereas the United States has 48 states and 160 million people, Great Britain has a population of about 50 million and is the size of Minnesota.

Another significant fact to remember is that the general practitioner is *not* permitted to care for his patients in the hospital but must refer them to the specialist who then assumes care of the patients and returns them to the general physician upon discharge. This procedure, of course, disrupts the continuity of care and does not stimulate interest on the part of the general physician.

Two arguments expressed in favor of the system were that the general physician did not miss the continuity, and that the system in the United States caused the general physician to overstep his training or ability. In refutation I noted that the younger men were against this old tradition; that Dr. Charles Fleming, the principal medical officer for Scotland, wrote an extensive treatise regarding the need for that change and others corresponding to United States practice; and finally that both instances are dependent upon the integrity of the man and his recognition of his own limitations.

In so far as medical training and postgraduate training are concerned, the students are for the most part of high caliber and well trained. The medical care, training, research, and plans in the teaching hospitals are comparable to the United States. However, in general the equipment and facilities, though adequate, are not comparable. A number of nursing homes are used by the general practitioner and his consulting specialist. Surgery and obstetrics are performed in these homes, but very few, if any, laboratory procedures. Thus, the hospitals are government owned and administrated. Therefore, it is evident that there are 2 basic segments to medicine in Great Britain: (1) the general physician in home care without the use of a hospital, and (2) the specialist in hospital care. The effect these situations have played in the socialization scheme will be noted.

An impression is gained that a great deal of good together with bad and potential dangers are present in the scheme, but that each indi-

JAMES ROGERS FOX, *a 1946 graduate of the University of Minnesota Medical School, is an internist at the University of Minnesota Health Service and a member of the faculty of the School of Public Health.*

vidual personally must see the needs and application to the country to understand its evolution. In no instance can any phase of medicine in Great Britain be compared with that in the United States.

In Great Britain socialized — or nationalized, as they prefer to call it — medicine really began in 1911 as the panel system, whereby the government began to pay physicians for the care of some patients. For many years only those who earned less than 400£ a year were included. This amount was equivalent to $2,000 but possessed a greater buying power. The program was carefully thought out and further extensions were planned. The Conservative Party, not the Labor Party as we have believed, was the originator of the program and was in the process of consultation with the British Medical Association, when the Labor Party through Bevan made the program a political football and, with votes in mind rather than British health, thrust it through. The rapidity with which the program passed was aided by the poor cooperation of the voting conservative population. The cost was estimated in 1948, when the plan was begun, at 510 million dollars. The mechanism was to be simple and it is, for the basic plan had been in effect for thirty-seven years. However, the cost in 1951 was 1.3 billion dollars and about 1.5 billion dollars for 1952. The Conservative government set a 1.2 billion dollar limit per year thereafter. However, it can be seen that some of the problems are being met, but slowly. Thus, as I have been told, "when we get the rough edges off and are used to the scheme, it will not be so bad."

The plan is compulsory for all and is directly under the control of the government with local subdivisions. Physicians are *not* in control. The plan is paid for either directly to the government, or by the usual deductions if the person is on a payroll. The fee for all social benefits includes an amount for the plan which, if calculated by population, will not in itself run the program into the black. The panel system involves the general practitioner. The general physicians are not centralized, but rather tend to care for the patients in their own area. Thus, it was simple to continue this tradition. To become a panel member, the patient merely signs up for a year with the doctor of his choice. The number of patients is limited to 3,500 per doctor, having been cut from 4,000, and includes children. The system does not permit the doctor to see more than this number of patients. Thus, the patient's choice is somewhat restricted. However, could a general physician care for 3,500 people as often as they desire in a year? With better than 90 per cent of Britain now gainfully employed, some patients, who formerly had to wait their turn, now will pay to be seen. With this increase in private practice, the doctor is not supposed to show discrimination, but as one man said "human nature frequently prevails." The adjustments made in the past years include that of an increase in fee and decrease, by 500, in the number of patients per physician. Currently the pay is $2.38 per head per year for the first 500, $3.78 for the next 1,000, and $2.38 for the remaining 2,000, which totals about $9,700. If a physician has a certain number of patients, he can now obtain through the Health Service an assistant who receives a straight salary of about $2,000. Some of the original problems appear to be combated on the surface, but others take their place. With the increase in fee and decrease in patient load to the general practitioner, the specialist group was up in arms for an increase. The training of students and paying of salaries of about $5,000, which corresponds to the amount our senior residents are paid, has increased the number of specialists to the point where there are not enough hospital positions, and they are not accepted in general practice. The increase in employment has worked to the advantage of private-paying practice as noted. With the bureaucracy of the Health Service, as I was told by a physician high in the government service, several major problems have resulted. (1) Because of the disadvantage of being a general physician, most students intend to specialize. I noted this fact personally while a member of the University of Edinburgh faculty. (2) The general physician now has little opportunity to specialize, for he finds it impossible to get a position while training. (3) The general physician may not change jobs as he desires. In order to establish practice in a community, he must apply to the Executive Council whose members are not physicians. He cannot set up practice unless the council feels the area lacks physicians. Thus, the freedom of practice location is no longer free! (4) In addition, fewer general physicians are striving for advance degrees — a fact particularly true in the past. A gradual decline of general practice was predicted with the one redeeming note being that an Academy of General Practice has been formed.

Some general physicians, particularly in industrial areas, enjoy the Health Service remuneration, for they did not have it in the past. Most of those with whom I talked at length felt they had compromised themselves.

The specialist is not paid in the same manner as the general physician, but instead generally

has an appointment to one of the hospitals where he is paid according to the number of sessions he works — a total of 11 sessions are possible at $560 each. In addition, he may make up to 50 domiciliary calls at $12 each, a total of about $6,800. However, he may and does see private patients in consultation. In addition, 35 per cent of the specialists receive "merit awards" each year ranging from $1,400 to $7,000. Reputedly there is a fair manner of selection, but there is also the human equation!

From another authority I learned that the established specialists were faring remarkably well, but that the newer men were receiving positions on a straight salary only, and that the intent of the government circles was to place them all under civil service, which then would negate what few bargaining rights are left. Medical facilities, equipment, and the like are improving, but this is due largely to the fact government control has relaxed on rationing material and construction with resultant new building.

The specialists' problems, besides those previously noted, include the fact that there are too many specialists for the number of positions. As a result, in Great Britain as well as in the Scandinavian countries, most junior staff men are usually in their forties. Other examples of bureaucracy are these: in attempting to get a man for a position in a hospital, the chief may not hire whom he desires, but must show first the need, and then take it through the chain of hospital command, administrator, executive council, district council, regional council, and finally headquarters. Another is that if a physician obtains funds for a research project and then notes that the project will not succeed, he cannot divert the remainder of the money to another phase of research. He must return it. The outcome needs no explanation.

It must be remembered that in previous years hospital appointments were without salary, but rather for the prestige and referrals. Now the specialist is being paid for what had been done gratis.

Hospitals are now catching up with the old backlog of elective procedures after almost six years of extended waiting lists. This is true because patients are over the novelty stage and because so many use private insurance schemes to have more personal care in private rooms at nursing homes. In addition, a very few of the better nursing homes, originally left out of the plan, are being included. Moreover the Royal College laboratories for outpatient or nursing home use, which were not supported by the government, are now being used. This makes the care in the home or nursing home far more desirable, although the average number of laboratory procedures done by physicians in Scotland is only 27 in a year.

The patient pays for nothing in the hospital, not even drugs, laboratory tests, and so forth, and is discharged to the care of his personal physician. Dentistry is free, but restricted — a financial advantage is to pull all teeth and make dentures. Prostheses are free if necessary for livelihood, but now there is a charge for the wig and toupee.

Compensation to the worker is separate from the health service. Public health measures, particularly tuberculosis control, have improved in the past two years but are far from adequate. Only 7 per cent of expenditures go to these public health needs. Another problem has arisen in the form of free legal counsel and as a result the health service is being sued along with the physician, since he is employed — even for actions that occurred years earlier. This situation results in further expenditures — if only for defense purposes.

At present a study commission is examining the problems and needs of the health service and the country. It does not have a physician in its number!

Many opinions and reasons are given by the numerous proponents, opponents, and acceptors of the plan in each of the categories of patient, doctor, government, and press, which I shall not elaborate upon. However, there is much dissatisfaction and this situation, even in the face of satisfaction to many, indicates that even to the British the plan has not improved adequately.

Tuberculosis Case-Finding Programs in Colleges

Twenty-third Annual Report of the American College Health Association Committee on Tuberculosis for the Academic Year 1952-1953

A REVOLUTION is occurring in the management of tuberculous disease. After Hinshaw and Feldman demonstrated in 1944 that Waksman's streptomycin was effective in altering the course of this disease,[1,2] even effecting cure in cases which had rarely, if ever, been cured before, tuberculosis therapy has been rapidly improving. Perhaps, after studies now underway in many clinics are completed and reported, we will have even more effective specifics which will cure all but the most advanced cases of tuberculosis.

The fact must constantly be remembered, however, that no case of tuberculosis can be treated unless it is first discovered. Furthermore, success with the newer forms of treatment, as with the old, is inversely related to the length of time the disease has been present and the degree of involvement when therapy is begun — the longer it has been present and the more extensive the disease, the less effective the treatment.

Success of case-finding programs is built upon the triple concept that (1) the disease must be discovered before treatment can be started; (2) the earlier the diagnosis, the better the chance for recovery; (3) the earlier the diagnosis, the less the possibility of spread. These recommendations of the American College Health Association Committee on Tuberculosis,[3] have held almost without change for more than twenty years and are as valid today as ever before. It may be true that fewer active cases are being discovered on most campuses than in former years.

Likewise, if evaluated on the basis of the number of cases discovered compared to the time, effort, and cost, probably the results are statistically unconvincing. The fact remains that cases of tuberculosis are still being reported. The possibility is a constant threat to the health of a campus community. For years to come those who have become infected by an unknown and probably unsuspected case living among them will have a totally unnecessary hazard added to their problem of health maintenance.

We believe that all members of the campus community should be surveyed at regular intervals for signs of tuberculosis. The disease is communicable and is no respecter of individuals,

TABLE 1

NUMBER AND PERCENTAGE OF AMERICAN COLLEGES AND UNIVERSITIES WHICH ANSWERED QUESTIONNAIRES, AND PERCENTAGE WHICH REPORTED TUBERCULOSIS CONTROL PROGRAMS, CLASSIFIED BY ACADEMIC YEAR

Academic year ending June 30	*Colleges sent questionnaire*	*Replies received*		*Colleges which reported programs*	
		Number	*Per cent of colleges sent questionnaires*	*Number*	*Per cent of replies received*
1953	1,068	721	67.5	564	78.2
1952	1,068	672	62.9	548	81.5
1951	1,050	495	47.1	422	85.3
1950	880	578	65.7	500	86.5
1949	880	*	*	448	*
1948	889	438	49.3	374	85.4
1947	885	311	35.1	259	83.3
1946	883	507	57.4	362	71.4
1945	885	461	52.1	312	67.7
1944	886	400	45.1	286	71.5
1943	879	398	45.3	267	67.1
1942	850	488	57.4	311	63.7
1941	854	483	56.6	304	62.9

*Data not available in blank columns for 1949.

TABLE 2

COLLEGES SENT QUESTIONNAIRES, REPLIES RECEIVED, AND TUBERCULOSIS CONTROL PROGRAMS REPORTED, CLASSIFIED BY GEOGRAPHIC DIVISION AND STATE FOR THE ACADEMIC YEAR ENDING JUNE 30, 1953

Division and state	Colleges sent questionnaires	Replies received	Programs reported	Annual increase (+) Annual decrease (−) in programs reported
UNITED STATES AND TERRITORIES	1,068	721	564	+16
NEW ENGLAND	96	64	52	−5
Connecticut	14	9	6	−2
Maine	8	6	5	−1
Massachusetts	47	34	30	
New Hampshire	8	4	3	
Rhode Island	8	5	5	+1
Vermont	11	6	3	−3
MIDDLE ATLANTIC	179	112	91	−4
New Jersey	22	14	12	−1
New York	83	44	33	−10
Pennsylvania	74	54	46	+7
EAST NORTH CENTRAL	190	149	125	+13
Illinois	51	40	36	+8
Indiana	27	22	17	−4
Michigan	25	20	17	
Ohio	56	42	35	+7
Wisconsin	31	25	20	+2
WEST NORTH CENTRAL	134	102	72	+4
Iowa	24	15	9	−4
Kansas	22	17	13	−2
Minnesota	20	15	15	−2
Missouri	30	24	15	+7
Nebraska	18	14	10	+3
North Dakota	9	6	5	+1
South Dakota	11	11	5	+1
SOUTH ATLANTIC	173	108	81	
Delaware	3	3	2	−1
District of Columbia	13	6	4	
Florida	11	9	7	−1
Georgia	26	17	11	
Maryland	22	13	8	−2
North Carolina	33	19	17	+3
South Carolina	21	8	6	−1
Virginia	27	19	16	+3
West Virginia	17	14	10	−1
EAST SOUTH CENTRAL	83	48	36	−1
Alabama	18	9	7	+2
Kentucky	19	9	3	−2
Mississippi	15	8	8	−1
Tennessee	31	22	18	
WEST SOUTH CENTRAL	96	50	39	+3
Arkansas	14	10	9	+1
Louisiana	18	9	9	+3
Oklahoma	17	11	9	
Texas	47	20	12	−1
MOUNTAIN	38	27	19	−3
Arizona	3	2		−1
Colorado	11	10	10	+1
Idaho	4	4	2	
Montana	6	5	5	+3
Nevada	1			
New Mexico	7	3		−4
Utah	5	2	1	−2
Wyoming	1	1	1	
PACIFIC	76	60	48	+9
California	44	35	28	+4
Oregon	16	14	12	+4
Washington	16	11	8	+1
ALASKA	1			
HAWAII	1	1	1	
PUERTO RICO	1			

TABLE 3

TUBERCULOSIS CONTROL PROGRAMS REPORTED BY TYPE OF PROGRAM AND GEOGRAPHIC DISTRIBUTION, ACADEMIC YEAR ENDING JUNE 30, 1952

Division and state	Programs reported: Total	X-ray	Tuberculin testing	Combined program
UNITED STATES AND TERRITORIES	564	467	51	46
NEW ENGLAND	52	48	1	3
Connecticut	6	5		1
Maine	5	4		1
Massachusetts	30	29	1	
New Hampshire	3	3		
Rhode Island	5	5		
Vermont	3	2		1
MIDDLE ATLANTIC	91	78	5	8
New Jersey	12	11	1	
New York	33	27	2	4
Pennsylvania	46	40	2	4
EAST NORTH CENTRAL	125	94	17	14
Illinois	36	29	3	4
Indiana	17	13	3	1
Michigan	17	16	1	
Ohio	35	23	5	7
Wisconsin	20	13	5	2
WEST NORTH CENTRAL	72	51	11	10
Iowa	9	5	3	1
Kansas	13	6	4	3
Minnesota	15	11	1	3
Missouri	15	13	1	1
Nebraska	10	10		
North Dakota	5	2	1	2
South Dakota	5	4	1	
SOUTH ATLANTIC	81	71	8	2
Delaware	2	2		
District of Columbia	4	4		
Florida	7	7		
Georgia	11	9	1	1
Maryland	8	8		
North Carolina	17	15	2	
South Carolina	6	6		
Virginia	16	15		1
West Virginia	10	5	5	
EAST SOUTH CENTRAL	36	34		2
Alabama	7	6		1
Kentucky	3	2		1
Mississippi	8	8		
Tennessee	18	18		
WEST SOUTH CENTRAL	39	32	4	3
Arkansas	9	9		
Louisiana	9	8		1
Oklahoma	9	6	2	1
Texas	12	9	2	1
MOUNTAIN	19	14	2	3
Arizona				
Colorado	10	8	1	1
Idaho	2		1	1
Montana	5	4		1
Nevada				
New Mexico				
Utah	1	1		
Wyoming	1	1		
PACIFIC	48	45	2	1
California	28	26	1	1
Oregon	12	11	1	
Washington	8	8		
ALASKA				
HAWAII	1	1		
PUERTO RICO				

either as to age, sex, race, color, economic status, or social position. Since the danger is best known to the medical, nursing, and allied professions, the health service staff is obligated to acquaint their campus associates with the importance of an all-inclusive tuberculosis program. This is in keeping with the theme of the Fourth National Conference on Health in Colleges held in New York, May 5 through 8, 1954, which stressed interdepartmental cooperation to further the cause of student health.

Over the years the number of colleges report-

TABLE 4

COLLEGES HAVING STUDENT HEALTH SERVICES AND PHYSICIAN IN CHARGE, CLASSIFIED BY GEOGRAPHIC DIVISION AND STATE FOR THE ACADEMIC YEAR ENDING JUNE 30, 1953

Division and state	*Colleges with student health service*	*Physicians in charge*
UNITED STATES AND TERRITORIES	674	530
NEW ENGLAND	55	45
Connecticut	9	8
Maine	4	4
Massachusetts	28	23
New Hampshire	3	2
Rhode Island	5	3
Vermont	6	5
MIDDLE ATLANTIC	100	90
New Jersey	12	12
New York	39	34
Pennsylvania	49	44
EAST NORTH CENTRAL	142	108
Illinois	36	29
Indiana	21	16
Michigan	20	13
Ohio	40	35
Wisconsin	25	15
WEST NORTH CENTRAL	98	62
Iowa	15	7
Kansas	17	10
Minnesota	15	10
Missouri	22	18
Nebraska	14	7
North Dakota	5	3
South Dakota	10	7
SOUTH ATLANTIC	104	92
Delaware	3	2
District of Columbia	5	4
Florida	8	7
Georgia	17	14
Maryland	12	10
North Carolina	19	18
South Carolina	8	8
Virginia	19	18
West Virginia	13	11
EAST SOUTH CENTRAL	44	32
Alabama	8	8
Kentucky	8	3
Mississippi	8	8
Tennessee	20	13
WEST SOUTH CENTRAL	48	36
Arkansas	9	7
Louisiana	8	6
Oklahoma	11	6
Texas	20	17
MOUNTAIN	27	22
Arizona	2	2
Colorado	10	8
Idaho	4	3
Montana	5	3
Nevada	0	0
New Mexico	3	3
Utah	2	2
Wyoming	1	1
PACIFIC	55	42
California	32	25
Oregon	13	10
Washington	10	7
ALASKA	–	–
HAWAII	1	1
PUERTO RICO	–	–

ing some type of tuberculosis control program has steadily increased. The academic year 1952-1953 was no exception, with 16 more colleges reporting programs than in 1951-1952, a comparison of 564 to 548 (table 1). This is always a source of encouragement for the Tuberculosis Committee, although we are convinced that others besides ourselves are also instrumental in stimulating interest in tuberculosis control on college campuses. Many colleges are unable to carry on such a program, either administratively, financially, or both. Very frequently an official or a voluntary health agency, health department or tuberculosis association, has offered to assist a college in the organization of a satisfactory tuberculosis survey. We trust this relationship will continue and that colleges lacking adequate facilities will appeal to their local health department or tuberculosis association for assistance.

SURVEY PROCEDURE

In August 1953, a double postcard type of questionnaire was mailed to 1,068 colleges, with the following request:

TUBERCULOSIS remains a constant threat to all. An active and continuing program of CASE FINDING protects the INDIVIDUAL and safeguards the GROUP.

Would you please, once again, fill out and return the attached card? We wish to continue our cumulative record of the extent to which AMERICAN COLLEGE STUDENTS are protected against this unnecessary disease. A prompt reply will be appreciated. Thank you.

Max L. Durfee, M.D., Chairman
Committee on Tuberculosis
American College Health Association

The following information was requested on the return postcard:

Institution . . . . . .
Address . . . . . .
Do you have a Student Health Service? Yes . . No . .
Is there a physician in charge? Yes . . No . .
Name of Health Service Director . . . . . .
Did you have a TUBERCULOSIS CONTROL PROGRAM in 1952-53? Yes . . No . . Directed by . . . . . .
If Yes, check method used in your TUBERCULOSIS CONTROL PROGRAM.
(1) Tuberculin skin test with x-ray of reactors . . . . . .
(2) X-ray alone as initial screen . . . . . .
(3) Both tuberculin skin test and x-ray initially . . . . .
Information furnished by . . . . . .
Name and Title

TABULATION OF DATA

Data obtained from the reply postcards have been summarized in tables 1 through 4 which are appended to this report.

Table 1 shows the number of colleges answering the questionnaire, as well as the number of colleges reporting case-finding programs.

Table 2 analyzes the replies by geographic division and state.

Table 3 shows the types of programs reported each year, by geographic distribution.

Table 4 shows the colleges which reported having a student health service and those with a physician in charge. These figures represent an increase over those of the previous year,

when 616 colleges reported a student health service and 516 reported a physician in charge.

We wish to express appreciation for the services of the National Tuberculosis Association in mailing the questionnaires and tabulating the data.

Respectfully submitted,

ADVISORY TO TUBERCULOSIS

J. Burns Amberson, M.D.,
Bellevue Hospital, New York City
Robert J. Anderson, M.D., chief,
Division of Chronic Diseases and Tuberculosis,
Public Health Service, Washington, D. C.
J. Arthur Myers, M.D.,
University of Minnesota, Minneapolis, Minnesota
Floyd Feldmann, M.D.,
National Tuberculosis Association, New York City
Esmond R. Long, M.D.,
The Henry Phipps Institute, Philadelphia, Pennsylvania
Henry Sweaney, M.D., Chief Medical Director,
Florida State Hospital, Tampa, Florida

COMMITTEE ON TUBERCULOSIS

Max L. Durfee, M.D., *chairman*,
Oberlin College
William M. Brace, M.D.,
University of Michigan
Ralph I. Canuteson, M.D.,
University of Kansas
H. D. Lees, M.D.,
University of Pennsylvania
J. Edward Johnson, M.D.,
University of Texas
Otto J. Keller, M.D.,
Northern Illinois State
Teachers College
Charles N. Lester, M.D.,
University of Washington

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We have arrived at the cold war stage of the struggle with tuberculosis, and it has many likenesses to the cold war in the international field. Both lack the spur of win-or-lose combat which arouses enthusiasm. Diplomats can't feel as heroic going to a conference where they will inch along by argument as when they march off with a regiment but, unheroic as they may feel, they can't let this feeling interfere with their alertness, tenacity, or industry . . . . There is danger that, in the cold-war stage of the campaign against tuberculosis, we may lose the zest which our pioneers felt in grappling with death.

George J. Wherrett

Edward Allen Boyden

Author, Renowned Anatomist, and Beloved Teacher

J. ARTHUR MYERS, M.D.
Minneapolis, Minnesota

When a man so lives and works that his contributions to knowledge are recognized everywhere, that man's life deserves to be recorded in numerous places where many others can familiarize themselves with his character, methods of approach, and tenacity of purpose. Such a man is Edward Allen Boyden, born in 1886 in Bridgewater, Massachusetts, of Pilgrim and Puritan stock. He had an unusual educational heritage in that his grandfather served as president of Bridgewater, Massachusetts State Teachers' College for forty-six years, until 1906, and his father held this position from that time until his death in 1933. Allen graduated from this school one year after his father became president.

Allen's leaning toward zoology can be attributed to his father, who was especially interested in natural science. Two years after leaving the Bridgewater school, Allen received a B.S. degree at Harvard — magna cum laude — and in 1911 a M.S. degree. The next year he spent at the Institute of Anatomy in Freiburg, Germany, where he became especially interested in medical anatomy. Returning to Harvard as a teaching fellow in the medical school, he pressed forward for the Ph.D. degree in medical sciences, which was granted in 1916. He was then immediately appointed instructor in anatomy, and three years later he was advanced to an assistant professorship. During these thirteen years on the Harvard teaching staff, he was granted two brief leaves of absence to teach and do investigative work, one at Leland Stanford University, and the other at the University of California.

In 1926, he was called to the University of Illinois College of Medicine as associate professor, then professor of anatomy. In 1929, the medical school at the University of Alabama was in need of reorganization, and Dr. Boyden was chosen to reorganize the department of anatomy. When that division was well in order, he accepted a professorship in anatomy at the medical school of the University of Minnesota in 1931, where he remained until his retirement in 1954.

From 1912, when he became a teaching fellow in anatomy at Harvard until he retired as head of the department of anatomy at the University of Minnesota in 1954, Dr. Boyden was thoroughly appreciated by the thousands of students whom he taught. Harold S. Diehl, dean of medical sciences, University of Minnesota says, "Over the many years that Dr. Allen Boyden has been a member of the staff of the University of Minnesota Medical School he has typified the finest type of faculty member." But during these forty-two years he was continuously engaged in investigative work. He used the time that might have been idled away seeking information and contributing knowledge. His long nights, week ends, holidays, and even some vacations were devoted to this cause.

It is of interest that Allen Boyden's work on the extrahepatic biliary tract began in 1922 with the finding in a cat of a pancreatic bladder which had grown up alongside the gallbladder from an accessory pancreas. Previously, embryologists had considered that the anomalous pancreatic bladder arose from a splitting of the gallbladder and bile ducts. Allen noted that the pancreatic bladder was contracted and the gallbladder distended. Wishing to

compare sections of the two organs in the same physiologic state, he began feeding cats egg-yolk and cream and discovered that the gallbladder could be completely emptied by what later became known as the "Boyden meal." When Evarts Graham visited Boston in December, 1924, to describe his new technic, Allen immediately asked his colleagues in roentgenology to give him the Graham-Cole test and to x-ray his gallbladder after a meal of egg-yolk and cream. These pictures, demonstrating complete emptying of the human gallbladder, were shown by Whitaker at the 1925 meeting of the American Medical Association in Atlantic City (see figure 4, J.A.M.A. 86:239, 1926). Thus began a series of studies that were to be of great importance not only to anatomists and physiologists, but also to roentgenologists in diagnosis and to clinicians in both medical and surgical treatment.

As antimicrobial drugs became available, as anesthesiology improved, as liberal use of blood was employed, and surgical technics advanced, the chest began to yield its secrets to the surgeon. Allen Boyden's contribution to segmental anatomy of the lungs — a subject which taught the surgeon that individual diseased segments could be removed without sacrificing an entire lobe or a lung—was significant. In the foreword of Dr. Boyden's book, Evarts Graham writes: "Everyone with an interest in the subject may congratulate himself that an anatomist of the caliber of Edward Boyden has devoted his energies to the production of this classic work." Boyden's interest in this subject began in February, 1945, when Owen H. Wangensteen, chief of surgery at the University of Minnesota, asked him to appear before a staff conference to discuss the segmental anatomy of the lungs. Although Brock's fundamental work had appeared, no adequate "maps" of the lungs had been included in the literature to show the relations of bronchi, arteries, and veins in the different lobes; so Allen hurried to make some preliminary dissections prior to appearing before this conference. His first paper on this subject was published in December of the same year, in *Surgery*, edited by Dr. Wangensteen. Thereafter, for nine years, a series of original articles appeared analyzing the variations in the segments. Brock, in his edition of 1954, wrote: "The only sound way to conduct a proper inquiry into the matter is that undertaken by Boyden and his associates whose results have been published in a notable series of papers. . . . I shall draw heavily on their work in writing of the variants." So did the German surgeon Zenker in his book, "Die Lungenresektionen."

Dr. Leo G. Rigler, chief, department of roentgenology, University of Minnesota, says, "The contributions of Dr. Edward Allen Boyden to the field of roentgen diagnosis are the most important of those of any living anatomist."

Owen H. Wangensteen, chief, department of surgery, University of Minnesota, says, "In my opinion, Allen Boyden is one of the great students of anatomy of his generation. He has left his impress upon this province of knowledge as well as upon this Medical School."

While at Harvard, he examined 10,000 mammalian livers at the abattoirs in the vicinity of Boston. There he met and conversed with "kosher cutters" from local synagogues, who informed him that the anomalies for which he was searching had been described in the Babylonian Talmud and its codifications. No analytic survey of this material was available. He could not read the Talmud. So, after coming to Minnesota, he contacted S. I. Levin, Senior Rabbi of Minneapolis, and interested him in translating the anatomic portions of the sixteenth century codification, the Shulchan 'Aruch. Rabbi Levin and Dr. Boyden devoted one night every week to the study of this source material. Then with the help of proper dictionaries, it was put into literal and philologically correct form in which root meanings of anatomic descriptions were faithfully adhered to. Finally, a sample chapter was submitted to the department of Semitic languages in Harvard University. When this was approved, arrangements were made with the University of Minnesota Press to publish the translation. This appeared in 1940 and the entire edition was promptly sold. Those who have spent an evening or more with Dr. Boyden have been fascinated with his charming description of this chapter in the history of medicine.

Dr. Boyden has published more than 100 articles, mostly in medical journals. His book entitled, "Segmental Anatomy of the Lungs, A Study of the Patterns of the Segmental Bronchi and Related Pulmonary Vessels," which appeared in February of this year is the first of its kind. It is packed with important new information which is indispensable to students, teachers, and clinicians.

In 1928, he became managing editor of *The Anatomical Record* and edited the next 62 volumes. Concerning this work, Charles H. Denforth recently said, "Few not on his board, and those only to a degree, could have been aware of the effort that went into shaping these volumes into the monument that they are. The critical reading of each paper, the pertinent questions, the helpful suggestions, the firm but sympathetic restraint on the over-enthusiastic, the immature, and the ill-informed have born real if intangible fruit, for here, no less than in the classroom and the seminar, Dr. Boyden has been, as he continues to be, a potent influence in shaping the quality and the direction of American anatomy."

He has also been a member of the editorial board of *Acta Anatomica* since 1946.

In 1943 he was president of the Minnesota Pathological Society. He served as a member of the executive committee of the American Association of Anatomists from 1939 until 1945, as first vice-president from 1946 to 1948, and as a member of the committee on nomenclature since 1946.

In 1928, the University of Illinois awarded him the William Beaumont Prize; and in 1937, the Southern Minnesota Medical Association presented him with its Gold Medal.

On his first trip to Europe he met Miss Margaret Hilsinger. They were married in 1913. Their daughter, Mary, graduated in medicine at the University of Minnesota and is a prominent pediatrist in Lawrence, Kansas. Their son, Arthur, is manager of one of the departments in the Minnesota Mining and Manufacturing Company and resides with his wife and two children in St. Paul, Minnesota.

Dr. Boyden is an exceedingly calm and kindly person. Many medical students after completing courses in anatomy, have written him or called upon him personally to express their appreciation of his many kindnesses and excellent teaching. He has always been ready to help every student and especially those who had not quite adjusted to their courses. The following is one of many examples. The son of a physician had not done well during the freshman year. The father consulted Dr. Boyden, who immediately and continuously offered encouragement and direction to the student whose medical course went smoothly thereafter. Today this former student is an outstanding surgeon. The number of students helped in some such manner will never be known, for Dr. Boyden's modesty forbids.

Dr. Boyden came to the University of Minnesota in 1931, on the invitation of Dr. C. M. Jackson, who, as chief of the department, had become one of the most outstanding anatomists in America. When Dr. Jackson became totally incapacitated in 1941 and was confined to his home for several years, Dr. Boyden called on him every week to make certain that everything possible was provided for his comfort and welfare. After Dr. Jackson's death in 1947, Dr. and Mrs. Boyden looked after Mrs. Jackson as they would a member of their own family, until they moved from Minnesota in 1954.

When Mrs. Boyden became incapacitated, Dr. Boyden carried on with his work, but devoted every possible minute to her encouragement and comfort and had a nurse in constant attendance during the four and one-half years of her illness.

The editorial board of *The Anatomical Record* and his other friends in anatomy produced a Boyden Birthday Volume, which included four numbers, January to April 1954. The first article, entitled, "In Honor of Edward Allen Boyden" contains a more detailed account of his life and work than is presented here. The remainder of this volume is composed of excellent articles mostly on anatomic subjects.

Immediately preceding Dr. Boyden's retirement, his friends contributed to a fund of the Minnesota Medical Foundation. This was invested in the seminar room in the department of anatomy, for the purpose of reflecting Dr. Boyden's interest in this room as a center of the life of the department. Among other items, a displayed placque is in the room with the following inscription: "In honor of

Reproduction of bookplate made from an original oil painting.

Edward Allen Boyden, Professor and Head of the Department of Anatomy, University of Minnesota." Another, reproduced in this article, is a bookplate made from an original oil painting by Edward Brewer of St. Paul. Prints of this are attached to the 275 volumes which Dr. Boyden gave to the department of anatomy. On May 18, 1954, 150 of his friends assembled at the Campus Club for dinner in his honor before his retirement in June.

When his retirement became known, a number of schools desired his postretirement service. The University of Washington was fortunate in his acceptance of a visiting professorship in anatomy. There he is continuing his fine teaching and research. On January 5, 1955, he wrote, "All is going well here. I couldn't have come to a place where I would have been happier."

The American Association of Anatomists elected Dr. Boyden as one of three delegates to participate in the meetings of the International Congress of Anatomy to be held in Paris in July 1955. Enroute he will spend a week in London where he has been invited to lecture in Brompton Hospital.

His excellent contributions have been so important that wherever teaching and research are conducted in anatomy, wherever diagnostic and therapeutic work are done, particularly on the gallbladder and the lungs, the name, Edward Allen Boyden, resounds and will continue to do so through the generations.

Lancet Editorial

Tuberculosis and the Private Physician

Tuberculosis today stands at the crossroads. Whether the disease will continue to fall and eventually disappear or whether it will, like so many of our other communicable diseases, continue to smolder along in small foci sheltered from the public interest remains largely in the hands of persons reading this issue of The Journal-Lancet and others concerned with the problem. With the rising costs and decreasing yields of mass x-ray film surveys and with the falling death rate, the tuberculosis control officer is faced with the dilemma concerning the future. Should he largely neglect tuberculosis, presuming that the mortality rates will continue to fall and that the disease is of negligible public importance, or should he search for new tools and adapt them to the eventual aim of eradication of this disease?

In the search for new tools and the re-evaluation of old ones, the revitalization of the tuberculin test as a case-finding and epidemiologic tool is impressive. From the apex of regard as a therapeutic and diagnostic tool shortly after its discovery by Koch in 1897, opinion of the tuberculin test had fallen by the year 1938 to the extent that it was considered of questionable value even to demonstrate past infection. The reason for this fall lay in undue reliance on the x-ray film as a differential diagnostic tool. Thus, when the radiologist stated that calcified lesions were due to tuberculosis, and when the tuberculin test was found to be negative, the logical assumption was that the tuberculin test was not a satisfactory tool for demonstrating past infection. This fall in the prestige of the tuberculin test, however, had a markedly beneficial effect in that careful evaluation of this test resulted. In re-evaluating the test on various groups of different exposure to tuberculosis, Furcolow and associates[1] were able to establish that the tuberculin test was indeed a very satisfactory tool for the demonstration of past or present infection with the tubercle bacillus. Also quite suprisingly low rates were demonstrated in tests throughout the country among young adults. Most important of all, an intermediate dose of tuberculin proved satisfactory for diagonstic use, and nonspecific reactions occurred when larger doses, such as the ordinarily employed second-strength dose, were used.

The demonstration of the efficiency of a single intermediate testing dose and the low prevalence of reactors among general population groups brought a new realization of the value of the tuberculin test. Although this information has been rather slow in being disseminated to the profession, the fact is now widely realized that less than 15 per cent of persons even in large midwestern cities are positive to tuberculin by the age of 20. Moreover, the use of a single testing dose rather than 2 doses has resulted in more widespread application of the test by physicians. This has raised urgent questions which remain unanswered such as: What is the value of the tuberculin test as a case-finding tool? What is the cost to find cases of tuberculosis by follow-up of positive tuberculin reactors? Such studies are underway in Minnesota and in Kansas City, Missouri, and other places.

Of great practical importance to the private physician is the question of his place in the problem of tuberculosis control. The ideal tuberculosis control program would return to the private physician the primary responsibility for diagnosis and treatment. Certainly the trend is toward the return of the treatment to the private physician, usually supervised or assisted by sanatorium physicians or other specialists. In the field of diagnosis, however, the difficulties of employment of the cutaneous test have retarded many physicians from applying it routinely in their offices. Also the longstanding misconception that almost everyone is positive to the tuberculin test has deterred this universal application.

Tests in county-wide surveys in Minnesota have demonstrated a surprisingly low prevalence of reactors among the population as a whole. In several surveys, around 22 per cent of the entire population appear to be positive to the tuberculin test. In Kansas City surveys, approximately 30 per cent of the population were estimated to be positive to the tuberculin test. This figure is quite surprisingly low in view of the fact that Kansas City is a large industrial city.

Perhaps we might turn for a moment to the future and visualize an ideal program of tuberculosis case-finding. This would entail the use of a simpler test than the intracutaneous — a test such as the patch, ointment, or some such simple test which a physician could easily apply to all of his patients. He would thus separate his patients into 2 groups — positive and negative. The positive group would be followed by x-ray films at different intervals depending upon their age. While strict criteria cannot as

yet be set out, the breakdown rate differs with different ages, and the frequency of x-ray films among those positive would vary with the danger of breakdown. Obviously older persons would require more frequent films, from the points of view of both tuberculosis and carcinoma. Among the tuberculin-negative patients, frequent tuberculin tests would be applied, perhaps as often as several times a year. The finding of a positive reaction in a person previously negative would be a signal for immediate action. This would consist of a follow-up by the official health agency of the contacts of this individual in an attempt to determine where the infection had been acquired. Meanwhile the physician might treat this patient for a period with some simple drug as a preventive against the development of serious tuberculous disease, or he might watch the patient's progress carefully with the idea of treating him should clinical lesions develop.

While we are far from the realization of such a program, it is not beyond the realm of possibility that such tools will be available in the near future. A rational start toward such a program at the present time would be to envision more widespread use of the tuberculin test by physicians in their practices and in schools, with some encouragement such as *certification* to secure maximum participation. Coincident with the widespread application in the schools, certain areas should undertake experiments with county-wide surveys in an attempt to uncover all, or almost all, of the foci of tuberculous infection in their county. Some method of county-wide certification might be useful in this regard. Several forward-looking areas in Minnesota and in Kansas have already made preliminary steps toward such a county-wide tuberculosis clean-up. With these county-wide surveys, the necessity of repeated testing in order to continually uncover foci of tubercle bacilli must be kept in mind.

Finally, the physician concerned with tuberculosis and diseases of the chest must always be aware of the complications arising from fungous infection of the lungs which may simulate tuberculosis in every degree. A recent demonstration of histoplasmosis as an etiologic factor in bilateral pulmonary cavitation necessitates a re-evaluation by those who have been relying on x-ray films for diagnostic purposes. Luckily, accurate and satisfactory diagnostic tools for the diagnosis of the most prevalent fungous infection in the middlewest, namely, histoplasmosis, are available. It is of interest to note that skin testing, even in such areas as Minnesota, reveals a higher prevalence of positive histoplasmin skin tests than of positive tuberculin skin tests. This is mentioned simply to highlight the diagnostic importance of skin testing. With histoplasmosis the interpretation of the positive skin test is the same as that with a positive tuberculin skin test; namely, past or present infection. In addition, in histoplasmosis, serologic tests are available which are positive only during the active stages of the disease. We have, therefore, with histoplasmosis satisfactory diagnostic tools for both the presence of infection – the skin test – and activity of the disease – the serologic test.

Therefore, adequate diagnostic tools appear to be available to the physician for the purpose of separating this disease from other infections.

Finally, all physicians should be alerted to the fact that case register loads of active tuberculosis are higher now than at any time in the last few years. With the improved therapy of tuberculosis, case loads obviously will continue to be heavy for some time. Tuberculosis, therefore, is far from being a conquered disease. Physicians should regard it as a duty, both in their practice and in their public utterances, to push for adequate and complete eradication of tuberculosis with whatever tools are feasible and available.

Michael L. Furcolow, M.D.

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Physicians Must Play Their Role

In the history of man, the present moment offers the greatest hope for the ultimate eradication of tuberculosis. This, the most serious disease scourge of mankind since the dawn of history wreaked destruction among animals and people almost unabated until the twentieth century A.D. It long ran neck and neck with malaria as an incapacitator and life taker. With the advent of insecticides and other methods of malaria control, tuberculosis remains the first cause of incapacity and death among the 2,400,000,000 people of the world.

In a few small places on the world map, including the Scandinavian countries and the United States, phenomenal accomplishments have been made during the last few decades. Apparently good diagnostic procedures, prevention of spread of both bovine and human types of tubercle bacilli, and employment of the best known treatment have played an important role.

The microscope, the tuberculin test, and the x-ray film, together with the conventional physical examination, resulted in early diagnosis of the disease. The sanatorium and the hospital prevented much spread of tubercle bacilli. Bed rest, localized rest accomplished by collapse therapy, antimicrobial drugs, and resectional surgery have been effective thera-

peutic procedures. Control of tuberculosis in animals, particularly cattle, has also been of tremendous value.

With these methods in use, unprecedented declines occurred in such places as Iceland, Puerto Rico, and the United States. In Iceland, tuberculosis mortality rates dropped from 216 per 100,000 in 1930 to 9 in 1953; in Puerto Rico, from 302.7 in 1934 to 38 in 1954; in the United States, from nearly 200 in 1900 to 12.3 in 1953.

These methods have also tremendously reduced the incidence of primary tuberculosis – tuberculous infection – among children and young adults. An excellent example is the report in this issue of THE JOURNAL-LANCET by Krug and Glenn, Pennsylvania State University.

Over the greater part of the world where these methods have not been employed in more than a minor way, the decrease in tuberculosis mortality was slight until 1947, when a precipitous decrease began to appear wherever antimicrobial drugs were extensively used. Apparently, because of the drugs, more patients with tuberculosis are living today than would have been alive without them. This situation may be only temporary since it is not yet known whether the effects of drugs are permanent. Some workers wonder whether many persons whose lives have been extended by chemotherapy will later require hospitalization and finally die from tuberculosis.

In any event, in areas where mortality, morbidity, and infection attack rates have decreased so phenomenally, there is now the opportunity to refine the methods of attack and strike directly at the tubercle bacillus rather than just at the gross disease it produces.

The first step in the development of tuberculosis is the initial invasion with tubercle bacilli. No matter at what age in life this occurs, there is no way to predict whether the microscopic lesions produced will remain small and benign or will ultimately progress to clinical and even killing proportions. The problem is simplified in that, (1) primary invasions can be detected by the tuberculin test within a few weeks after they occur, (2) methods are available for the detection of clinical lesions which evolve before they have caused much destruction or have become contagious, and (3) therapeutic methods are available which are capable of controlling such lesions so they do not cause illness or become contagious. It may even be possible to destroy all tubercle bacilli with antimicrobial drugs if administered soon after the invasion occurs, thus preventing subsequent development of clinical lesions. Even if such sterilization does not prove possible, we still have an exceedingly effective method of periodically examining tuberculin reactors and treating clinical lesions as they appear.

The incidence of persons now harboring tubercle bacilli varies greatly in different parts of the world. In nations with large populations where little effective tuberculosis control work has been done, so many children become infected that nearly all adults possess at least lesions of primary complexes containing tubercle bacilli. Among such people, a correspondingly high incidence of clinical tuberculosis is present.

At the opposite extreme are parts of the world such as Scandinavia and the United States, where effective tuberculosis control measures have been operating for several decades and where relatively few children and young adults now harbor tubercle bacilli. However, in such areas tuberculin testing has revealed that as many as 60 per cent of the persons in the later decades of life are infected with bacilli which they probably acquired as children before adequate protective measures were in operation. By testing entire populations with tuberculin, tubercle bacilli can be located. Thus, the magnitude of the present and future tuberculosis problem in that population is determined. A spot map of a given area, such as a township, county, or state can be made indicating every home in which 1 or more persons are infected with tubercle bacilli. Billions of tubercle bacilli are in each of these homes. Such a map has been made of 1 county in Minnesota and is to be exhibited at the meeting of the National Tuberculosis Association in Milwaukee in May. In that county about 1 person in 5 is infected with tubercle bacilli, most of whom are beyond the age of 40 years. This does not mean that 1 in 5 homes is marked on the map, since in some homes several members of the family are infected.

The item of importance is to learn where tubercle bacilli are being harbored and act accordingly. Immediate examination of tuberculin reactors usually identifies those who have contagious tuberculosis and prompt action terminates further spread of their tubercle bacilli. Reactors who are not found to have clinical tuberculosis may at any later time have this disease, but periodic examinations should detect it before it is contagious and adequate treatment in most cases keeps the tubercle bacilli corralled in their bodies.

Tubercle bacilli in older persons usually reside in lesions which are necrotic so that they probably cannot be reached by drugs in the blood stream. Therefore, our only recourse is to keep these organisms corralled for the remainder of the individual's life. This is a slow, tedious method, but is the only one now available. However, the procedure is much faster than allowing contagion to develop before the disease is detected and setting up tuberculous foci in the bodies of the young, thus increasing and complicating the problem.

In its later phases, tuberculosis is often a contagious disease and, thus, may be the problem of every citizen. Therefore, tuberculosis eradication should become a community project everywhere. Only professional workers are trained to conduct diagnostic procedures and administer treatment. Other persons may participate in various ways such as dissemination of information. Such cooperation can ultimately eliminate tubercle bacilli.

In Meeker County, Minnesota, the medical profession set out to control tuberculosis in 1941. They instituted a countywide demonstration. During this demonstration period, they made the necessary time and effort a gift to the citizenry of the county. No charge was made for administering and reading the tuberculin test, exposing, developing, and reading x-ray films, or completing examinations when indicated. The actual costs of material such as x-ray films were paid by cooperative organizations. This demonstration revealed that about 22 per cent of the citizens, mostly older people, were harboring tubercle bacilli. Among them, 16 were found to have clinical tuberculosis.

This public service greatly increased the confidence of the citizenry in its medical profession. It demonstrated that local physicians were capable of doing modern tuberculosis work. It squelched those who believe and teach that physicians are interested only in fees.

During the demonstration period, the public was informed that all persons who did not react to tuberculin should have the test repeated at least annually, while all who reacted during the demonstration or subsequently should be examined at least once a year for the detection of clinical lesions which might evolve.

Ever since the demonstration closed, a great many people from Meeker and adjacent counties have gone periodically to the physicians to have tuberculin tests, x-ray films repeated, or whatever was recommended.

The question is not whether physicians of a county or a state can afford to put on such a demonstration gratis, but rather that they cannot afford to overlook such an opportunity. It is an excellent way of securing and maintaining confidence, good will and support of the citizenry. These are the factors which are so needed in returning the greater part of the tuberculosis problem to the offices of local physicians, particularly those in general practice. When this is accomplished we may expect the most effective attack of all time upon the tubercle bacillus.

There are approximately 90,000 physicians practicing general medicine in this country. They have organized the American Academy of General Practice, with state and local chapters. They can now work as a unit. An ideal example of such work is that of the St. Louis Academy of General Practice with approximately 200 members. In 1951, this Academy adopted as its main project tuberculin testing in St. Louis schools. That work is described in part in this issue by Walter C. Gray, chairman of the Committee on Tuberculosis of the St. Louis Academy of General Practice.

It is to be hoped that soon many and ultimately all such organizations, as well as county and state medical associations, will become tubercle bacillus hunters and track down, corral, and ultimately eliminate the last tubercle bacillus.

At this moment, it is exceedingly important that the decrease in the number of new cases of clinical tuberculosis evolving and the precipitous decline in mortality are not interpreted as the approach of immediate ultimate victory over tuberculosis. Such an interpretation could play into the hands of the tubercle bacillus, which could soon again become as widespread and destructive as it was in this country fifty years ago. The phenomenal success in reducing morbidity and mortality represents a battle less than half won against the tubercle bacillus.

As physicians we must gird for a long, tedious fight with refined methods capable of locating every person now harboring tubercle bacilli. These persons must be examined promptly and those who already have progressive clinical disease must be dealt with immediately. The remainder, which constitutes the majority, of those now harboring tubercle bacilli must be examined periodically as it is among them that a crop of clinical tuberculosis must be harvested annually. Only by harvesting this crop at the proper time can we keep tubercle bacilli corralled for the remainder of the lives of their hosts.

J. Arthur Myers, M.D.

Section on PAIN

Comments concerning this Section, criticisms, or suggestions for papers will be most welcome. Physicians are cordially invited to submit articles pertaining to pain for consideration. All inquiries and manuscripts should be sent to Dr. John S. Lundy, 102 Second Avenue Southwest, Rochester, Minnesota, or to the Editorial Department, THE JOURNAL-LANCET, *84 South Tenth Street, Minneapolis, Minnesota.*

Some Physiologic Mechanisms Underlying the Manifestations of Acute Abdomen*

KHALIL G. WAKIM, M.D.

Rochester, Minnesota

THE PROBLEMS presented by the clinical entity "acute abdomen" challenge the surgeon, internist, and physiologist alike. Only after the abdomen is explored is some light shed on these problems. However, laparotomy is apt to raise just as many and as important questions as it answers. It is essential to keep in mind that nonsurgical and surgical conditions of acute nature may coexist, either related or independent of each other. Severe diabetic acidosis and acute suppurative appendicitis, or myocardial infarction and a saddle embolus at the bifurcation of the abdominal aorta, are good examples of such coexistence.

CAUSES OF ACUTE ABDOMEN

The clinical entities which give rise to acute abdomen are appallingly numerous but, for the sake of orienting the reader, a partial list will be given here:

(1) acute appendicitis; (2) perforated peptic ulcer; (3) acute cholecystitis; (4) perforation of ulcerative colitis or ulcerating carcinoma; (5) diverticulitis; (6) regional enteritis; (7) pancreatic disease, especially acute pancreatitis; (8) intestinal obstruction; (9) mesenteric vascular occlusion; (10) peritonitis; (11) renal disease, especially renal calculi; (12) tubo-ovarian disease, such as ruptured corpus haemorrhagicum, ruptured tubal pregnancy, acute salpingitis, and twisted pedunculated ovarian or uterine tumor; (13) certain acute traumatic injuries leading to perforations in the gastrointestinal tract and compression, laceration or rupture of spleen, liver, kidneys, or bladder; (14) certain acute physiologic aberrations resulting from uremia, diabetic acidosis, Addison's disease, acute leukemia, Henoch's purpura, myocardial infarction, pericarditis, dissecting aneurysm of abdominal aorta, gastrointestinal hypersensitivity of allergic origin, chronic lead poisoning, and acute porphyria; (15) neurologic disorders, such as gastric crisis of tabes, herpes zoster, and intercostal neuralgia.

CLINICAL MANIFESTATIONS OF ACUTE ABDOMEN

Certain symptoms contribute toward the development of the clinical picture of acute abdomen. Arranged in the order of frequency of occurrence, the following make a partial list of the important clinical manifestations of acute abdomen:

(1) Pain, whether referred or unreferred, is the most frequent complaint of the patient with acute abdominal

KHALIL G. WAKIM, *a graduate of the American University of Beirut, is professor of physiology in the Mayo Foundation and consultant, section of physiology at the Mayo Clinic. He has been civilian consultant to the office of the Surgeon General of the United States Army and the Army Medical Center on basic medical education and research since 1948.*

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disease. (2) Tenderness is also common. (3) Nausea, vomiting, and anorexia mar the picture. (4) Spasm, rigidity, abdominal splinting, and abdominal distention are fairly common. (5) Shifting dullness, absence of peristalsis (ileus) or hyperactivity of the intestine (obstruction) are often associated with the condition.

The obliteration of liver dullness, which sometimes is observed in acute abdominal conditions, is explained by the pneumoperitoneum revealed by roentgenograms of the abdomen. When the patient sits up in bed, the air may accumulate under the diaphragm, irritate it, and bring about the annoying condition of hiccups.

PAIN IN GENERAL

Of the foregoing important clinical manifestations of acute abdomen, the outstanding complaint is pain. It is pain, therefore, with which this article is primarily concerned.

Certain changes of adequate intensity occur in the external or internal environment as a result of which sensory end organs are stimulated and afferent impulses are set up. The afferent messages sent to the nervous system as a result of sensory stimulation bring about reflexes to extinguish the stimuli and maintain the organism in a state of readiness to cope with other changes that might occur in its environment. Pain is one of those disturbances manifesting damage to the body and setting up certain bodily reactions in order to abolish it, or at least to minimize it.

Very little is known of the way in which the various kinds of pain arise or how they involve the higher centers of the nervous system. However, some important facts have been established regarding the peripheral mechanism of pain. Pain is produced by stimulation of the naked nerve terminals which end freely. Some[1,2] suggest that sharp, well-localized pain is due to the rapid-conducting myelinated fibers and that the dull, aching, poorly localized pain is due to the nonmyelinated slow-conducting fibers. However, there is no convincing evidence to support this idea.

ABDOMINAL PAIN

Referred abdominal pain in general. Referred abdominal pain can be adequately explained by the fact that some visceral afferents converge with cutaneous pain afferents to end at the same spinothalamic tract neurons, and the impulses, upon reaching the brain, are interpreted as having come from the skin. This explanation is based on previous experience which indicated that the same tract fibers were stimulated by cutaneous afferents. The posterior roots contain many more pain fibers than the spinothalamic tract, consequently several pain fibers must converge upon one tract fiber. This makes it very likely that a number of afferent pain fibers coming from the diaphragm, for example, will converge with cutaneous pain fibers entering the same segment to join some of the spinothalamic tract neurons. In the light of the doctrine of specific nerve energies, no matter where they originate, impulses along spinothalamic tract fibers are identical. These impulses are responsible for conveying messages from the body surface. Consequently, even though the impulses may be visceral in origin, upon reaching the cerebral cortex, they are interpreted as pain arising from cutaneous areas.

The question of the reality of visceral pain will be discussed briefly in a moment, but it is necessary to refer to it here. Morley[3] recognizes the concept of true visceral pain but ascribes referred pain to inflammation of the parietal peritoneum. His peritoneal cutaneous reflex may give a valid explanation for the referred pain in visceral disease of inflammatory origin, but this explanation is inadequate for the pain referred to the surface of the body in noninflammatory conditions.

PARIETAL TYPE

Referred parietal pain. This pain has been demonstrated by stimulation of the diaphragm. When the margins of the diaphragm are stimulated, the pain is referred to the anterior abdominal wall which is supplied by the same thoracic nerves. Stimulation of the central zone of the diaphragmatic pleura or peritoneoum produced pain which was invariably referred to the shoulder and neck. This wide discrepancy between the point of origin and the area of reference of the pain can be reconciled easily by the fact that the diaphragm migrated caudally and its nerve supply went with it.

Unreferred parietal pain. Capps and Coleman[4] passed a wire into body cavities and applied pressure or friction to visceral and parietal structures. They found that the visceral peritoneum covering the organs was insensitive to this form of stimulation, but stimulation of the body wall caused sharply localized pain originating in the body wall over the site of stimulation. This pain was not referred and the nonreference was presumed to be due to the innervation of superimposed areas on the inner and outer surface of the body wall by the same posterior nerve root.

VISCERAL TYPE

Is there any such thing as visceral pain? Two misconceptions contributed to the belief that viscera were insensitive: (1) the idea that the autonomic nervous system contained no afferent fibers, and (2) failure to appreciate the principle of adequacy of the stimulus.

Mackenzie[5] suggested that autonomic impulses aroused in a diseased visceral organ would set up an "irritable focus" upon entering the spinal cord and cause excitation of cells accustomed to receive impulses from the corresponding somatic area. Therefore, impulses originating in viscera are relayed to cells of the corresponding somatic area. From this somatic center new impulses travel along the usual paths to the higher perceptive centers in the thalamus, which refer the sensation to the skin or muscle of that somatic area from which the impulses are customarily received. Mackenzie designated the resulting pain in the superficial structures as "viscerosensory reflex" and the referred motor reaction in the form of rigidity and hypertonus of muscles over the diseased organ as "visceromotor reflex." The hyperesthesia and hyperalgesia, with tenderness to touch, pressure, or light pinching of the skin, are due to impulses received by the hyperirritable segment in the cord from the diseased visceral organ.

Mackenzie[5] denied the existence of visceral pain. He believed that afferent autonomic impulses aroused in diseased visceral organs are incapable of arousing any sensation. Kinsella,[6] however, demonstrated that pressure on an inflamed appendix or over a duodenal ulcer causes pain centered in that viscus. The dullness, diffuseness, and poor localization of visceral pain are due to the characteristics of protopathic sensibility which is the only type of sensation carried by visceral afferents.

Morley[3] stated that referred pain arises only from irritation of nerves which are sensitive to those stimuli that produce pain when applied to the surface of the body, namely, by stimulation of somatic sensory nerves. He did not agree with Mackenzie[5] regarding the involvement of autonomic afferents in the referred pain of visceral disease. He expressed the belief that referred pain is due to stimulation of somatic pain fibers in the parietal peritoneum or mesentery and that the sensation is referred to the superficial area innervated from the same spinal segment. Morley[3] substituted "peritoneocutaneous radiation" and "peritoneomuscular radiation" for Mackenzie's[5] terms, "viscerosensory and visceromotor reflexes," respectively. The true visceral pain that was denied by Mackenzie[5] was well recognized by Morley.[3]

Pathways of visceral pain. Ordinarily this paragraph would introduce the section on visceral pain. Since the actuality of true visceral pain has been questioned, however, it seemed desirable, at the outset, to offer authority for believing that such pain exists.

Sensory impulses originating in structures within the abdominal cavity or thoracic cage may reach the central nervous system along 3 pathways: (1) by sympathetic nerves, (2) by parasympathetic nerves, and (3) by somatic nerves supplying the diaphragm and body wall. On the basis of connection with the central nervous system, visceral afferent impulses can be organized into 3 groups: (1) reflex afferent, which are not conveyed to consciousness and, therefore, arouse no conscious sensation; (2) organic sensation, which is believed to be conveyed to the central nervous system by way of the parasympathetic system exclusively; and (3) pain afferents.

Character and kinds. Visceral pain is usually described as boring, ill-defined, tending to be referred segmentally and not necessarily close to the organ originating it. Rubbing the undersurface of the diaphragm may elicit pain at the shoulder tip. Accurate localization of visceral pain is believed to be possible only after involvement of the parietal peritoneum by the disease process. Distention experiments by use of a balloon in the gastrointestinal tract of man have located above the umbilicus the pain arising from organs in the upper abdomen.

Visceral pain is either produced by stimulation of the inner surface of the body wall, or actually arises from the viscera themselves. Either type may be referred or unreferred. Some object to the designation "visceral" for the pain arising from irritation of the internal surface of the body wall. Even though this pain may not be strictly visceral, it is definitely an outcome of visceral disease. Invasion of the wall of the visceral cavities by the spread of inflammation, exudation, pressure, or friction will send pain impulses to the spinal cord along the somatic nerves supplying the walls of the body cavities.

Ross[7] divided pain from the viscera into 2 types: (1) referred (somatic) pain, and (2) true visceral or splanchnic pain. He described visceral pain as being diffuse, poorly localized, and felt in the viscus itself. Spinal segments supply visceral areas with autonomic fibers and

skin areas (dermatomes) with somatic nerves. The visceral and skin areas may be either closely related or very far apart.

Referred visceral pain. Pain originating in visceral organs is often referred to certain areas on the surface of the body a considerable distance away from the organ involved. Such pain is usually referred to the same dermatome whose posterior nerve root fibers convey the visceral afferents to the cord. The pathologic process of visceral disease is manifested by several physiologic mechanisms: (1) pain referred in type and dermatomal in distribution, (2) hyperalgesia, hyperesthesia; and tenderness, also dermatomal in distribution, (3) autonomic reflexes such as piloerection, sweating, or vasomotor changes, and (4) somatic reflexes including muscular rigidity and splinting. The intestine is embryologically a midline structure. Distention of the gut gives the same reference to the pain so produced, no matter whether the distended gut happens to be on the right or left side of the body.

Unreferred visceral pain. This is a deep, poorly localized pain. Ross[7] recognized the double nature of visceral pain and designated the unreferred component as "splanchnic pain."

Referred pain is not exclusively visceral nor does it indicate the existence of any unique properties of the visceral pathways for pain. The pain in deep muscles and deep viscera is referred and poorly localized. Faulty localization and faulty projection of deep pain are due to the lack of development of a topographically organized neural apparatus for localization and projection. The infrequency of deep pain and the inability to use vision to verify the source of stimulation lead to faulty projection to the surface. Lewis and Kellgren[8] obtained fairly accurate localization of irritants injected into superficial fascia, tendons, or periosteum of superficial bones, but the same structures, when deeply situated, gave diffuse pain which was regularly and reproducibly referred to a distant area of skin surface. Visceral pain and deep somatic pain were referred to the dermatomes innervated by the afferent fibers going to the posterior root which conducts the pain. Muscular rigidity and cutaneous tenderness accompany the referred pain of deep muscle irritation.

Pain originating in the intestine. The viscera[9] are exposed to stimuli quite different from those of the skin. Lennander[10] noted that the intestine could be cut, crushed, burned, or stretched without eliciting sensation. Distention with a balloon in the intestine could produce pain in man as well as in the animal. When Hurst[11] noted that distention and spasm of the human intestine caused pain and reflex changes, he suggested that tension in the intestinal wall is the only stimulus which affects pain nerve endings in the gut. He explained the apparent insensitivity of the gut to trauma on the basis of failure to apply adequate tension. Distention, chemical irritants, spasm, and strong muscular contraction, especially when accompanied by "ischemia," are effective visceral stimuli.

Lewis and Kellgren[8] could not elicit contraction of the abdominal muscles by pinching the intestine, but contraction was elicited by pinching the pancreas. This led Lewis[12] to suggest that the intestine lacks the afferent system of nerve fibers responsible for the reflex muscular activity. Downman and McSwiney[13] explained the absence of these visceral motor responses on the rapid disappearance of these reflexes when the abdominal cavity is disturbed or the intestine is frequently stimulated. They further suggested that the absence of a reflex action does not prove the absence of a pain-perceiving system but merely indicates a temporary loss of conduction in some part of the pathways. From work on animals Meyer[14] concluded that if the mesentery is protected from stretch, neither spasm nor distention can cause pain. Downman and associates[15] reported that chemical and mechanical agents were effective stimuli even though spread to the mesentery was prevented. By an electrophysiologic approach, in which they used amplifiers, they[16] found that trauma to the gut provokes impulses along fine fibers in the mesenteric nerves, which resemble the impulse pattern along fibers subserving pain sensation in the skin.

Epigastric distress. This condition is a frequent manifestation of the clinical picture of acute abdomen. Ivy[17] ably classified epigastric distress into the following:

1. Epigastric pain may be due to diseases residing in the stomach per se, for example, peptic ulcer, gastritis, gastric carcinoma, diaphragmatic or hiatal hernia, and duodenal ulcer.

2. Epigastric distress may result from diseases residing in other organs but reflexly affecting the function of the stomach, for example, epigastric pain of patients with appendicitis. It has been clearly shown that in patients with an appendiceal stoma, distention of a balloon placed in the appendix will produce epigastric pain caused by spasm of the pylorus and followed by nausea and vomiting. The onset of pneumo-

nia in children is often heralded by epigastric pain, with nausea and vomiting. Pyelitis and renal calculi in the pelvis or ureters are sometimes associated with reflex epigastric distress. Cardiac pain is often referred to the epigastrium. Myocardial ischemia and coronary insufficiency should be kept in mind.

3. Epigastric distress can be systemic in origin. In uremia of advanced nephritis, epigastric distress is one of the major manifestations.

4. Two types of functional epigastric distress occur frequently enough to deserve attention. One is dietary; the other is psychoneurotic. Dietary epigastric distress is best exemplified by the traveling business man who, in the course of a trip, eats large amounts of food rapidly, smokes and drinks plenty, and as a consequence develops a "sour stomach" with a strong feeling of fullness and severe, epigastric, cramping pain. A soft, bland diet and rest for a few days take care of such episodes. A roentgenogram of the stomach indicates no pathologic change in the stomach and the gastroscope may reveal some superficial gastritis, with reddening and edema of the gastric mucosa. Psychoneurotic states, with anxiety and tension over long periods, may become associated with symptoms of epigastric distress, with or without superficial gastritis and with or without gastric erosion. Prolonged anxiety states have been shown to cause organic lesions of the gastric mucosa.

5. Finally, epigastric distress may occur in patients with diseased organs of the epigastric region. Pancreatitis, whether of the relapsing or chronic type, is an excellent example. Determination of serum amylase is a helpful diagnostic aid. The pain of pancreatitis is often deep in the midepigastrium and more frequently is referred to the left than to the right. However, in the presence of disorder of the biliary tract, the reference is more to the upper right quadrant.

The splanchnics and surgical relief. Evidence suggests that a major role is played by the splanchnic nerves in the production of abdominal visceral pain. Foerster[18] reported that stimulation of the central end of a splanchnic nerve in man elicited unilateral pain. Bentley and Smithwick[19] abolished the pain on the same side of the midline in which the splanchnic nerves were resected. The pain elicited by distention of the gut is not altered by vagotomy.

By regional sympathetic denervation, White[20] was able to prevent this type of pain. He found that stimulation of the distal end of splanchnic nerves elicited no pain, but that pain was experienced deep in the chest and abdomen on electric stimulation of the central stump of the cut splanchnic nerve. He concluded that internal organs have definite sensitivity to pain, but their threshold is high and localization is poor. The ability for localization depends on the richness and overlapping of sensory nerve endings.[21] The mucosa of bodily orifices has a richer supply of pain terminals than the other visceral zones. Furthermore, no elaborate cortical projection is built up for the interior of the human body. White explains the poorly defined, dull, aching, deep visceral pain on the absence of the differentiated nerve endings that are capable of appreciating touch or temperature.

Lewis and Kellgren[8] reported the poor supply of pain-conducting fibers in the viscera and deep-lying structures such as skeletal muscles. They suggested that this poor supply is the basis for the need of massive stimuli to elicit pain in such localities. The presence of inflammatory reaction lowers the high threshold to pain of viscera and other deep-lying structures such as skeletal muscles, joints, and ligaments.

It is definitely recognized that visceral sensation is carried along afferent fibers which run with sympathetic motor axons in visceral nerves and finally enter the posterior roots and intermingle with somatic afferent fibers. The sympathetics transmit pain from the heart and abdominal viscera while the vagi carry sensation from the trachea and bronchi and from the esophagus. Morton and associates[22] have relieved the tracheobronchial irritation of carcinoma of the lungs by section of the vagi below the origin of the recurrent laryngeal nerves. Distention of the lower portion of the esophagus by balloon elicited pain after extensive thoracic sympathectomy.[23] This led to the conclusion that the vagus transmits sensation from the esophagus. White and associates[20,24] reported effective interruption of pain by specific sympathetic denervation of the heart, aorta, kidney, ureters, uterine fundus, and other abdominal viscera, provided the source of pain is confined within the capsule of the diseased viscus. However, if the pain has invaded somatic nerves, visceral and somatic spinal nerves must be interrupted. White suggested interrupting the secondary pain-conducting axons in the anterolateral quadrant of the spinal cord for the purpose of more extensive sensory denervation.

It is clearly shown that interrupting the splanchnic pathways along which the primary

impulses are transmitted to the central nervous system will do away with the pain. Bentley and Smithwick[19] could not induce pain by acute duodenal distention after splanchnicectomy. Bentley[25] demonstrated clearly that sensitivity of the gastric or duodenal wall to pressure was eliminated by splanchnic block anesthesia.

Visceral abdominal pain, with the exception of that from pelvic viscera, is carried chiefly along sympathetic nerves, very rarely, if at all, along parasympathetics. The regulatory reflexes essential for the function of visceral organs are not conveyed along the pain-carrying sympathetic afferents. Therefore, the function of organs denervated for the relief of pain is not seriously disturbed. In order to deprive a visceral organ of its pain fibers and relieve the patient of the pain, one of the following procedures advocated by various authorities should be done:

1. The artery supplying the area should be stripped of its nerves (periarterial neurectomy).
2. Ganglionectomy of the sympathetic chain should be performed at the proper level.
3. Several posterior nerve roots should be excised (rhizotomy).
4. The spinothalamic tract should be sectioned (cordotomy).

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Pain in Dental Disease

ROBERT J. GORES, D.D.S., AND R. QUENTIN ROYER, D.D.S.
Rochester, Minnesota

INFLAMMATION is one of the most important causes of pain in the oral cavity, and inflammation is consistently present within the soft tissues of the mouth. Periodontal disease (pyorrhea) and inflammation of the dental pulp are responsible for the great majority of oral maladies that produce intense pain. Few persons are free or have been free of these diseases. In still another category is the pain which occurs after surgical procedures in the mouth.

PAIN IN PERIODONTAL DISEASE

Gross neglect of oral hygienic measures is largely responsible for periodontal diseases. Oral debris consists for the most part of an accumulation of food deposits, desquamated epithelial cells, bacteria, and dental calculus collected in the gingival crevice. This subgingival calculus serves as an irritant which, in association with bacteria, produces inflammation of the gingivae. Inflammations of this type cause resorption of the bony alveolar crests, and, in consequence, deep bony and soft-tissue pockets or clefts are created along the sides of teeth. The deeper these pockets become, the more debris collects within them, thus enhancing the inflammatory process. A vicious cycle is thereby set up which literally melts away the bony support of the teeth. Pain in such circumstances is most severe when pus accumulates in these pockets and its escape is blocked at the gingival crevice. In essence, a subperiosteal abscess is formed and the pain is due to the stripping of the periosteum away from its bony attachment. Relief is obtained when the pus escapes by formation of a fistula or by means of incision and drainage.

A similar situation is set up around partially erupted teeth (pericoronitis). In such situations a communication is established between the oral cavity proper and the tissues which form a crypt around the partially erupted tooth. Debris accumulates in the crypt, inflammation of the surrounding tissue follows, and trapped pus produces tension on the surrounding structures. This results in severe pain for the same reasons as stated previously. Occasionally, instead of the formation of pus, cellulitis ensues. Cellulitis also is a most painful process because of the distention of soft tisue that is caused by inflammatory edema.

Vincent's stomatitis, trench mouth, or ulceromembranous gingivitis probably is the most common acutely painful gingival infection. The initial lesions occur in the gingival crevice adjacent to the necks of the teeth. Acute inflammation of the gingival interdental papillae follows. Necrosis ensues which destroys the interdental papillae. A pseudomembrane is formed which sloughs and causes denuded, ulcerated areas. Acute local pain is characterized by a constant, pulsating ache. This pain is aggravated by occlusion of the teeth, which feel loose and unduly long. Intake of even bland foods aggravates the pain.

PAIN IN DISEASE OF DENTAL PULP

Inflammation of the dental pulp and the sequelae of such inflammation produce the most severe pain encountered in oral disease. Dental caries, in its progress through the hard structure of the tooth, carries to the pulp microorganisms or their toxic products which produce inflammation of the pulp.

Inflammation of the dental pulp is exceedingly painful because the pulp is encased within unyielding walls of dentin, and the edema, which is a part of the inflammatory process, tends to increase the size of the pulp. The edematous pulp cannot expand because of its calcified encasement, and thus great pressures are exerted upon the many nerve endings within the pulp, stimulation of which is always interpreted as pain regardless of the nature of the stimulus. Hot and cold stimuli upon an inflamed dental pulp tend to exaggerate the hyperemia, and an increase in pain is experienced by the patient. This type of pain is not well localized by the

ROBERT J. GORES *is assistant to the staff at the Mayo Clinic.* R. QUENTIN ROYER *is with the section of dentistry at the Mayo Clinic.*

patient because the pulp itself has no proprioceptive nerve fibers.

The sequel to severe inflammation of the dental pulp is necrosis. The next event is extension of the inflammatory process through the apical foramen at the apex of the root of the tooth into the surrounding periodontal tissues. At this stage of the disease, the affected tooth becomes tender to percussion and therefore can be located.

After necrosis of the pulp has taken place, the application of heat to the affected tooth in many instances produces extreme pain, which can be relieved by a cold stimulus.

Hyperemia of the pulp often follows the necessary placement of a filling close to the pulp of a tooth. This stimulus is a mechanical one, and may not involve the entrance of microorganisms or their toxins into the pulp itself. This type of inflammatory process often is reversible and does not lead to necrosis of the pulp. The application of heat or cold upon a tooth thus affected produces a transient, sharp, lancinating pain due to the resultant hyperemia which is of the active type. When hyperemia is passive, thermal stimuli cause prolonged pain. In such instances the prognosis is more grave because the inflammation is not reversible and necrosis of the pulp follows.

Cementum or dentin that has become exposed to oral fluids as a result of gingival recession or retraction can be a source of pain which is similar to the pain experienced in pulpitis. Although the nature of the pain in exposed cementum or dentin is the same as that of pulpitis, the process is quite different. The phenomenon is not fully understood, mainly because nerve fibers have never been demonstrated to be present in dentin. The pain arising from the condition undoubtedly is a subjective symptom, in part varying according to individual variations in tolerance of pain. Exposure of dentin or cementum does not cause pulpal necrosis, but is most distressing to the patient when thermal shocks, such as cold air or hot and cold fluids, are encountered. Chemical stimuli such as acid, sour, or sweet materials also can cause the type of pain in question, which is sudden and sharp.

Inflammation in the maxillary sinus can cause a pain similar to that of pulpitis in the maxillary bicuspid or molar teeth because the inflammatory process in the affected sinus may encompass a nerve which innervates the dental pulp, thus producing a type of neuritis.

PAIN AFTER ORAL SURGICAL PROCEDURES

Severe postoperative pain accompanies complications such as: (1) a "dry socket" after simple extraction, (2) excessive postoperative edema associated with traumatic oral surgical procedures, or (3) postoperative cellulitis.

The "dry socket" occurs when the blood clot of a tooth socket is lost and the alveolar bone is left exposed to oral fluids which carry the oral bacterial flora. "Dry socket," or localized osteitis, thus develops. The pain is dull, continual, and severe.

Postoperative edema usually is encountered after the surgical removal of impacted third molar teeth. Edema fluid collects in loose arcolar tissues, and pain is caused by pressure of the accumulated fluid.

When postoperative cellulitis occurs, inflammatory edema fluid produces indurated tissue in the adjacent region. This causes extreme pain, discomfort, swelling, and trismus of the muscles of mastication.

SUMMARY

A brief review of the etiologic factors causing pain in and about the oral cavity has been presented. The review is limited to painful diseases of dentition and the supporting structures.

Editorial

OLD PAINS IN NEW DRESS

It is always interesting as well as instructive to read an article from an authoritative source concerning one of the commonest complaints of man; namely, "toothache." This may be regarded as a dental subject, yet there seems to be a real need for such an article in the literature that is available to physicians. Or, to put it another way, perhaps there is not yet enough exchange of interesting facts between members of the dental and the medical professions. Certainly the dental profession has much to teach us.

Moreover, a reader of this section ought to consider himself fortunate to have the opportunity to learn from a physiologist his views on, and his understanding of, the mechanisms involved in the complaints and symptoms associated with a condition known as the "acute abdomen," the signs and symptoms of which have not been too well understood in the distant past. Most of the descriptions and explanations of the patient's complaints thus far published have been made by persons other than those who are actually experts in physiology.

These are unusual papers from sources that are new to the practicing physician, and we are happy to present them in the Section on Pain of The Journal-Lancet. We venture to hope that more information from such sources may be forthcoming in the future, either by the voluntary generosity of an author or by direct request.

John S. Lundy, M.D.

Book Reviews on Pain

AIDS TO ANAESTHESIA, by Victor Goldman, L.R.C.P., M.R.C.S., lecturer in anaesthetics, Institute of Dental Surgery, London; consulting anaesthetist, Queen Mary's Hospital for the East End, London; Eastman Dental Hospital, London; and Battersea General Hospital, 1954. London: Baillière, Tindall & Cox. Third edition, 343 pages. Price $2.25.

This small book is precisely what it was intended to be—an aid to anyone who is interested in the administration of anesthetic agents. Nothing essential is overlooked. There are a few pages concerning the history of anesthesia and a few biographic sketches of the outstanding persons who have contributed to the improvement of anesthesia throughout the world.

The essence of the anatomic and physiologic implications of anesthesia is competently presented, as is the pharmacology of anesthetic agents. The stages of anesthesia are described and some very interesting advice is offered concerning the preparation of the patient for anesthesia. A chapter is included on inhalation anesthesia with the use of various agents, and a special chapter on nitrous oxide anesthesia, in which field the author is a master. Various relatively complicated technics of inhalation anesthesia are presented. There is a chapter on the use of vinyl ether, a natural inclusion, since the author is one of the outstanding physicians who major in dental anesthesia. Cyclopropane is mentioned. Intravenous anesthesia is discussed, and the technic of endotracheal anesthesia is dealt with in detail. Preliminary medication is outlined and the complications of anesthesia are explained.

There is a chapter on anesthetic agents for diseased patients and another chapter on anesthetic agents for special operations. The author reports on muscle relaxants and also on controlled hypotension. Anesthesia and analgesia in midwifery are accorded some space, but the best part of the book is devoted to anesthesia and analgesia in dental operations. Even a section on anesthesia in the tropics is included. A considerable portion of the book is devoted to local and spinal anesthesia.

An appendix gives a variety of interesting facts and information. The book is well indexed and is printed on good paper. It is easily read and can be carried in the pocket. This handy book should be available in every library and department of anesthesia.

John S. Lundy, M.D.

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FIRST AID AND RESUSCITATION, by Carl B. Young, Jr., M.P.H., instructor, Emergency First Aid; member, International Rescue and First Aid Association, 1954. Springfield, Illinois: Charles C Thomas, 338 pages. Price $8.50.

This book, written for those who have not had medical training, has been prepared with the hope that many lives will be saved by those who read it, because rarely is a physician present at the scene of an accident. All the accidents which are frequently seen are described, and treatment is outlined. The book is well illustratd. The book might well be considered required reading for those engaged in civil defense and for all who are concerned with first aid.

John S. Lundy, M.D.

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RESUSCITATION OF THE NEWBORN, by Joseph D. Russ, F.A.A.P., assistant professor of pediatrics, Tulane University School of Medicine; senior pediatrician, Touro Infirmary, New Orleans, 1954. Springfield, Illinois: Charles C Thomas, 55 pages. Price $2.50.

This book is based on the author's experience with 2,000 resuscitations from 1938 to 1953. He has divided the information into 5 sections. He defines and classifies the various types of asphyxia, lists the conditions interfering with the establishment of normal respiration, and gives some statistics on neonatal mortality. He discusses the pathologic processes found at necropsy, and includes photomicrographs of the patients' pathologic conditions.

This discussion is followed by the clinical factors, which are divided into 2 groups. In the first group are those factors existing prior to labor, and in the second are those factors occurring at the time of delivery. The analgesic and the anesthetic agents are discussed, and an extensive table is presented, prepared by Dr. John Adriani, in which are given the advantages and disadvantages to the mother and the effects on the baby of spinal anesthesia and anesthesia produced with Pentothal Sodium, ether, chloroform, nitrous oxide, cyclopropane, and Vinethene. This table is a fine addition to the book.

The author lists the miscellaneous causes of prematurity, postmaturity, erythroblastosis fetalis, and other conditions. He explains resuscitation and how the baby should be handled, the importance of the time element in resuscitation, the routine of resuscitation and the after-care, and mentions the drugs and machines that are used as artificial aids. He presents the after-effects of asphyxia, and, under the heading of education, urges the recognition of dangerous situations and an understanding of how to be prepared to handle them.

A bibliography of 139 references is found at the end of the book. It is well printed on excellent paper, can be easily read, and is of a convenient size. Those who must care for the newborn will find the book a welcome addition to their resources.

John S. Lundy, M.D.

Current Literature on Pain

USE OF NISENTIL HYDROCHLORIDE AS AN ANALGESIC DURING CYSTOSCOPIC PROCEDURES, by Lowrain E. McCrea, M.D., and Edward Post, M.D. J. Internat. Coll. Surgeons 21:480-483, 1954.

Nisentil hydrochloride (dl-alpha-1,3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride) is an effective analgesic for cystoscopic examinations because the analgesic rapidly controls pain and anxiety, yet leaves most patients awake and cooperative. After injection, the time before onset of analgesia is usually less than five minutes. The drug has a sedative effect of short duration, so the patient can usually walk out of the office after urologic examination.

Nisentil was administered intravenously in doses of 30 mg. in 0.5 cc. of solution to 100 patients from 16 to 83 years of age. Cystoscopic examination was successfully performed in 95, while 5 suffered side effects, including dizziness, vomiting, and 1 convulsive seizure.

In the 85 patients experiencing analgesia, the sedative effect lasted from two to sixty minutes, with an average duration of sixteen minutes.

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THE SURGICAL TREATMENT OF TRIGEMINAL AND GLOSSOPHARYNGEAL NEURALGIA: DECOMPRESSION OF THE GASSERIAN GANGLION AND ITS ROOT FOR TRIGEMINAL PAIN, by J. Grafton Love, M.D. J. Internat. Coll. Surgeons 21: 1-14, 1954.

Preservation of facial sensation while relieving pain of tic douloureux is accomplished with the trigeminal decompression technic. Previous methods of treatment have involved a high morbidity and mortality rate because of trauma to sensitive brain stem structures, postoperative cranial nerve palsies, loss of sensation in the cornea, and unexpected hemorrhage. The risks inherent in section of the trigeminal sensory root, avulsion, or medullary tractotomy can be avoided by the new extradural, transtemporal approach.

Studies of the gasserian ganglion have indicated that it may be compressed by small dural adhesions in older patients and that such bands may be responsible for the recurrences of pain after operation. The extradural approach is designed to decompress the ganglion and sever any adhesions while preserving the integrity of the sensory root. Since the dura is not opened over the brain itself, trauma to the temporal lobe is minimized and sensation is preserved over the face and cornea.

After trephination above the ear and ligation of the middle meningeal artery, the dura is stripped upward from the foramen ovale, away from the petrous ridge, and is incised over the posterior root and ganglion, leaving these structures completely free.

After the decompression procedure, the patients require much less nursing care and are able to leave the hospital within a few days. If pain recurs, the root may be divided through the same craniotomy. The transient facial weakness and herpes simplex which may occur respond well to symptomatic treatment.

Glossopharyngeal neuralgia is easily differentiated from tic douloureux by cocainization of the throat, which does not affect trigeminal pain. Section of the ninth nerve produces no significant motor or sensory loss and remains the treatment of choice.

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INTRACTABLE PAIN, by Frank Turnbull, M.D. Proc. Roy. Soc. Med. 47:155-156, 1954.

The detection and control of intractable pain necessitates a special organization under the direction of a medical or surgical neurologist. Intractable pain may be defined arbitrarily as continuing pain associated with incurable disease that requires at least 1 daily dose of a narcotic drug.

The most frequent cause of organic pain is advanced cancer. An orderly search must be made for the complications of cancer, but when all definitive treatment for the disease has been expended, pain should be regarded as a disease entity. The total terminal pain period constitutes the criterion for evaluating any particular kind of treatment. The administration of treatment for intractable pain should be under the guidance of a specialist just as is the organized therapy for cancer.

The plan of treatment which best suits any specific case of intractable pain must evolve from consideration of psychologic, sociologic, and medical factors. Every large cancer institute should have a special treatment clinic to plot the course of therapy after measures directed at the primary disease are exhausted.

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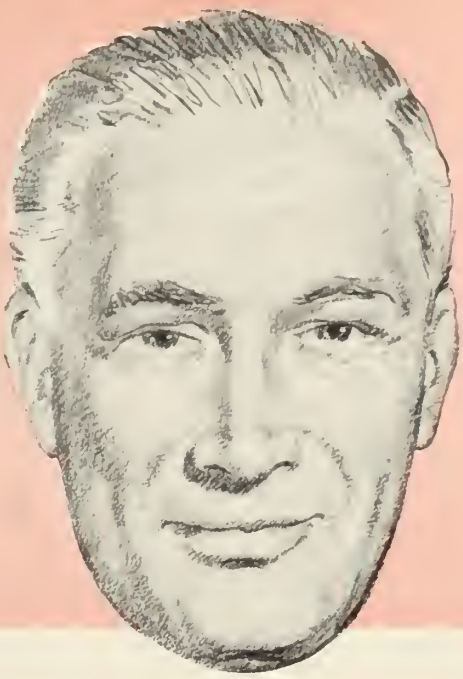

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BOOK REVIEWS

An Historical Chronology of Tuberculosis, by Richard M. Burke, M.D., 1955. Springfield, Illinois: Charles C Thomas. Second edition. 125 pages. $3.75.

This second edition lists the important events in man's struggle against tuberculosis from ancient times to the present. Chapter 1 is devoted to the ancient period, 5000 B.C.–1600 A.D. This includes Oriental and Hippocratic medicine, the post-Galenic era, and the Renaissance.

The premodern period is included in Chapter 2 and extends from 1600 to 1800. In Chapter 3, the first part of the modern period, extending from 1800 to 1881, is presented. The second part of the modern period, beginning with the discovery of the tubercle bacillus in 1882, is included in Chapter 4. This period extends to the present time.

Chapter 5 is devoted to milestones in the history of tuberculosis, the first of which was Hippocrates' accurate clinical description of phthisis, and the last which was the discovery of streptomycin, the first effective antibiotic against tuberculosis.

The first edition of this book did not contain a bibliography. However, the present edition includes 476 references selected from the world's literature on tuberculosis.

In his book entitled *Tuberculosis and Genius,* Dr. Lewis Moorman said that tuberculosis probably was the first-born of the mother of pestilence and disease. It has been man's greatest scourge from the dawn of history to the present time. The long battle between man and his domesticated animals and the tubercle bacillus with man on the losing side throughout the centuries but gaining ascendancy during the last few decades, is presented in a most fascinating manner in Dr. Burke's volume.

Every person, regardless of vocation, whose body harbors tubercle bacilli, whether or not he is ill from the disease, will find this volume most fascinating and entertaining as well as informative. It should be readily available to every physician, nurse, public health worker, and educator, as it is an accurate documentation of man's greatest enemy.

No one could have been better qualified to write this book than Dr. Burke. His personal experience with the disease, beginning as a medical student, his long years of continuous work in this field, including medical directorships of sanatoriums, private practice, presently teaching diseases of the chest to students of medicine and nursing at the University of Oklahoma School of Medicine, as well as directing the tuberculosis control activities of his entire state, and having written and published extensively on history and other aspects of tuberculosis, admirably qualified him for writing an historical chronology of tuberculosis.

J. A. Myers, M.D.

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Diseases Transmitted from Animals to Man, by Thomas G. Hull, Ph.D., 1955. Springfield, Illinois: Charles C Thomas. Fourth edition. 717 pages. $12.50.

This book has been a fine source of authentic information for the past quarter of a century. Thomas Hull and his expert contributors, of whom there are now 24, have done a fine service in keeping this book revised so it has always contained the latest and most authentic information. The present fourth edition is composed of 717 pages with 104 illustrations and 66 tables. The work of some 1,200 authors has been drawn upon in the preparation of this volume.

Few persons realize that now more

(Continued on page 35)

(Continued from page 32A)

than 100 diseases are transmissible from animals to man. Yet these diseases are all recorded in this volume with accurate documentary evidence, and the salient facts that are known about them. Chapter 1, by William H. Feldman, is an excellent presentation of tuberculosis transmissible from animals to man. The various types of tubercle bacilli from different animal hosts are discussed, and it is pointed out that from a public health point of view, tuberculous cattle constitute the most important animal source for tubercle bacilli that are virulent for man. Although, in the United States, bovine tuberculosis has been reduced to a remarkably low level, he says, "Yet so long as a single focus of infection remains, there exist the essentials necessary for the dissemination of the infection. The attack against the tubercle bacillus must be prosecuted with vigor and without compromise. An attitude of complacency, or one in which satisfaction with past achievements takes precedence over the importance of the task yet to be done will defeat any plan of approach, no matter how adequate it may appear to be." Feldman further points out that the remarkable achievements of the veterinary profession in practically eliminating tuberculosis in cattle in the United States constitutes a notable example for the guidance of physicians who are concerned with eliminating tuberculosis in human beings. He says, "The problem must be attacked nationally and with vigor, with the thought ever in mind that tuberculosis is a highly contagious disease."

The remaining 37 chapters of this book contain excellent accounts of anthrax, brucellosis, glanders, rabies, tularemia, and many other diseases known to be transmissible.

No veterinarian, physician, health officer, or other professional health worker should be without this book. Moreover, it should be in every public library, as it gives the general reader important facts about the magnitude of this problem and the importance of the general public in disseminating information guaranteeing everyone's support in control and eradication of these diseases.

J. A. Myers, M.D.

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Practical Fluid Therapy in Pediatrics, by Fontaine S. Hill, M.D., 1954. Philadelphia: W. B. Saunders Co. 275 pages.

Today, when more and more physicians are appreciating the tremendous importance in many cases of maintaining a proper balance between the electrolytes in the body fluids, and especially in cases in which there is too much or too little fluid in the body, many will be glad to see this book. For years it has been known that children and infants are particularly apt to die if things go wrong with their body fluids. As we all know, things can go wrong with their body fluids especially in cases of vomiting, diarrhea, pyloric stenosis, acute infections, kidney diseases, and burns.

In this book, a number of case reports are recorded. There is much on the physiology of the subject.

Walter C. Alvarez, M.D.

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Mental Health in the Home, by Laurence Spurgeon McLeod, Ph.D., 1953. New York City: Bookman Associates, Inc. 243 pages. $3.50.

The author has taught courses in mental hygiene for twenty-five years, and is now dean of the graduate division of the University of Tulsa. He believes that what is needed in the home is (1) honest self-appraisal, (2) the development of good work habits and a wholesome attitude toward work, (3) a proper regard for recreational activities, (4) proper respect for other people, (5) sound ethical standards and practices, (6) wholesome emotional reactions, (7) a good sense of humor, (8) a healthy response to occasional defeat, (9) honest religious practices, and (10) the creation of a healthy atmosphere in the home.

This book can help many people.

Walter C. Alvarez, M.D.

from an editorial in the J.A.M.A.
(156:991, Nov. 6, 1954):

Oral broad spectrum antibiotic therapy
may cause infection with Candida albicans

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A.C.H.A. News

SECTION ACTIVITIES

Dr. Grace Hiller, Goucher College, Baltimore, Maryland, reports on the National Conference on Health Education held in Washington, D. C., January 9 through 11, which she attended as a delegate of the A.C.H.A. The full title of the Conference, "National Conference on the Undergraduate Health Education Minor and the Desirable Health Education Emphasis for the Physical Education Major" indicated its purpose which was to recommend a desirable program for the health education minor and health emphasis for the physical education major. Colleges and universities from all parts of the country were represented by the 85 delegates who attended.

Mrs. Ruby Burgar, R.N., secretary-treasurer of the Pacific Coast Section has informed us that she has been requested by Dr. Lewis Barbato, chairman, Committee on Local Arrangements and Program, to moderate a nursing service group at the forthcoming Colorado Springs Meeting.

Mr. Richard G. Bond, chairman, Committee on Environmental Hygiene of the A.C.H.A. is compiling an inventory of personnel in student health work actively engaged in environmental health programs. All members will have received a letter by this time requesting their cooperation in this inquiry.

PERSONNEL

Dr. Norman R. Sloan, whose availability for student health work was reported in the December issue, has notified the secretary's office that he has accepted a position with the Hawaii Board of Health after he is released this summer from his present station on Canton Island in the South Pacific.

Several letters have been received in the past month from physicians interested in positions in the student health field. Any of our member colleges seeking personnel can obtain details by writing the Secretary-Treasurer, Dr. Irvin W. Sander, Student Health Service, Wayne University, Detroit 1, Michigan.

EXPANSION PLANS

Dr. C. G. Menzies, director, Health Service, writes us that authorization has been received from the Board of Agriculture to double the size of the Health Service facilities at Michigan State College, East Lansing, Michigan, at a possible expenditure of $2,000,000.

News Briefs . . .

North Dakota

Dr. Olof Larsell, former professor of anatomy at the University of Oregon College of Medicine and the University of Minnesota School of Medicine, is visiting professor of anatomy at the University of North Dakota School of Medicine for the present semester. Dr. Larsell is teaching neuroanatomy and completing his monograph on the cerebellum while at the University of North Dakota.

* * * *

Dr. C. J. Glaspel, of Grafton, was elected vice president of the federation of State Medical Boards of the United States at a recent meeting in Chicago.

* * * *

Dr. Martin Flom and Dr. Samuel Zinberg recently joined the medical staff of the Fargo Veterans Admin-

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

Thirty-five Years of American Pediatrics, 1919-1954

L. EMMETT HOLT, JR., M.D.

New York City

THE ROLE of the historian is an unaccustomed one for me. Most of us who lead busy lives have little time for history. We are sure it is important but not so very sure why, except from a general cultural point of view. I should like to submit that medical history has pragmatic value. In a rapidly evolving period of science such as we are now living in, the inflow of new knowledge tends to obscure the old, and valuable factual information is often lost and has to be rediscovered. It was known in the seventeenth century that ground-up oyster shells would often stop convulsions in infants, but it took a scientific age to rediscover the calcium treatment of tetany. To scan the road along which we have come may lead us to question the validity and the permanency of some of our present concepts and practices. And the study of trends may help particularly those of us who are teachers to make better forecasts as to the needs of tomorrow and the requisite training for them.

GOLDEN AGE OF MEDICINE

The period of the past thirty-five years which I have been asked to discuss covers the active life of both Dr. Irvine McQuarrie and myself. We were contemporaries in medical school at Johns Hopkins. We both came of age medically in what has been called the Golden Age of American Medicine. The career of the titan, William H. Welch, was drawing to a close. Scientific medicine had been brought to America. Cellular pathology was a virtually completed science. Bacteriology seemed to have nearly completed its task of discovering the agents of infectious disease. The principles of immunology seemed well established. In biochemistry, Emil Fischer had unraveled that most perplexing of the body's mysteries – that of protein structure. And what seemed to be the last of the major chemical riddles – the structure of nucleic acid – was rapidly giving way to the onslaughts of P. A. Levene and Walter Jones. Acid-base equilibrium and its regulation was well understood. The Golden Age seemed to have come. Ours was to be the task of practicing the newer medicine, of using the new tools. Of course, there was research to be done – no one could graduate from Johns Hopkins without an awareness of that – and it was the obligation of our generation to carry on. But the major discoveries seemed to have been made. The nuggets close to the surface had been picked up. The task of our generation would be largely a clean-up job; by dint of great effort we might be able to pick up a few crumbs.

How wrong we were, and how little we foresaw what the next thirty-five years would bring! In retrospect, it is we who have experienced the Golden Age, our predecessors only its first buds. There is scarcely a field of medical activity that has not been revolutionized in our lifetime. Today I will attempt to touch on only a few which seem to have done most to change pediatrics.

The pediatric house officer in today's modern

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

hospital would scarcely recognize his counterpart of World War I days. There were 4 or 5 times as many patients to look after but relatively little laboratory work to be done. Physical diagnosis was in its heyday. The expert physical diagnostician was the glamorous member of the attending staff whom all wished to emulate, the man who could recognize congenital syphilis from the facies and who could detect measles from the odor. Skill with an O'Dwyer intubation set was thought to be a prerequisite of every pediatrician, and spare moments were spent in practicing this art on cadavers. Opening eardrums was a daily occurrence, and every winter would bring its crop of retropharyngeal abscesses, to be opened by the sharpened fingernail of the expert pediatrician.

The roentgenogram was just beginning to be used for other than fracture cases; the first instrument which the Babies Hospital in New York City possessed was put in when I was a house officer in 1921. We had blood counts but no sedimentation rates. Routine blood chemistry was nonexistent. Some clinical bacteriology was done, the most rigorously followed procedures being a routine admission vaginal smear for gonococci on all girls and a routine admission throat culture for diphtheria. Skill with an intravenous needle in infants was an attribute not yet acquired. Fluid therapy consisted of saline hypodermoclyses, and, when blood had to be drawn for diagnostic purposes such as a Wassermann test, a barbarous procedure known as a Blackfan was employed at Johns Hopkins: a skin incision was made with a scalpel in the middle of the back, and the scalpel was moved about freely in various directions in the subcutaneous tissue to induce as much bleeding as possible. A suction cup with a dependent drain was then applied to collect the blood.

The house staff worked long and hard; they had no regular time off. They were unmarried and were supposed to be all-absorbed in their work, having no interest in the ladies. At Hopkins, house officers were strictly forbidden to go out with the hospital nurses. A sufficient hospital police force was, however, not available to enforce this rule.

ADVANCES IN PEDIATRIC PRACTICES

The diseases from which our patients suffered differed considerably from those we see today. Fully half of the babies admitted to the hospital had clinical evidence of rickets, and the remainder, if they came to autopsy, showed evidence of the disease almost invariably. There was no accepted treatment for rickets or for the tetany which so often accompanied it. Cod liver oil was sometimes given, in small doses without any great faith in its efficacy, and the tetanies went on having convulsions for days and often for many weeks.

The conquest of rickets was certainly one of the most notable achievements of the early years after World War I. It was the result of the combined efforts of 2 major departments at Johns Hopkins: the pediatric department under Howland and the biochemistry department in the School of Hygiene under McCollum. Park, who had been a member of Howland's team in Baltimore, continued to work closely with them after he moved to New Haven. It required the roentgenogram to demonstrate the efficacy of cod liver oil, the genius of McCollum to devise a diet that would produce rickets in the rat, and the microchemical technics devised particularly by Kramer to clarify the picture of what we now know as vitamin D deficiency. The final identification, in which the names of Hess, Steenbock, and Windaus figured prominently, did not come until after Howland's death.

The disappearance of rickets from the pediatric clinic began in the midtwenties as routine prophylaxis was introduced and, like most innovations, required a decade or more to be generally accepted. But, by 1940, rickets due to vitamin D deficiency was a matter of history. It is difficult for those of us to whom it was an everyday occurrence to share the excitement which the rare case seen today engenders in younger staff members.

The etiology of scurvy had been known for many years in the twenties, and yet we frequently saw clinical scurvy which today is as rare as rickets. Routine prophylaxis for one disease has made it easier to carry it out for another, and today we have the advantage of an army of pediatricians trained to carry out such procedures.

The decline of infant feeding is one of the most striking pediatric phenomena that has come since the twenties. Dr. McQuarrie and I were raised in an era when feedings for infants had to be most skillfully compounded, based on a meticulous daily scrutiny of the stools. The first duty of the pediatric resident in starting his morning rounds was to inspect a tray of stools and describe each in detail. Protein, fat, and carbohydrate had to be given in proportions suitable for the particular infant, not exceeding what was thought to be a narrow range of tolerance for each.

Intolerance to carbohydrates was the great bugbear of the day — too much carbohydrate

would cause a "blow up," with diarrhea and a precipitous weight loss. The glamorous feeding of the century for the infant with a digestive disturbance was Finkelstein's low-carbohydrate "protein milk." It was a great shock to me when I returned from my house training in New York to Baltimore in 1922 to find Dr. Howland actually adding carbohydrate to the sacred Finkelstein formula, and an even greater shock a few years later when Dr. Park came back to Baltimore to have him abandon protein milk at one fell swoop and feed a diarrhea baby a sweet-milk formula with 16 per cent added lactose! Lactose was regarded as the most dangerous of all carbohydrates from the point of view of fermentation, and the staff waited with bated breath for the blow-up that was sure to follow this heresy. The blow-up never came.

The major contributions to the simplification of infant feeding and the development of a single formula for all infants were probably made by Brennemann and Marriott. Brennemann appreciated more clearly than others the mechanical difficulties caused by the tough curds of unprocessed cow's milk, which caused minor symptoms of indigestion and — even more important — interfered with food assimilation. The problem could be solved in a number of ways; we do it now by heat processing. Marriott's important contribution was an appreciation of the fact that noninfectious or "simple diarrheas" were caused not by toxic materials from food but rather by parenteral infections. He did much to dispel the idea that formula specialization was needed and introduced what has since become our most popular infant food — evaporated milk.

The discovery that an infant could digest nearly any kind of food that was properly subdivided mechanically let down the bars for all kinds of solid foods and started the competition for their early introduction which we have with us today. How much of a gain this represents is debatable and has recently been debated. One thing is certain, however. The emphasis on digestion has in large measure been replaced by emphasis on nutrition. We have seen the science of nutrition unfold from the days when calories and calorigenic foodstuffs were the be-all and end-all. The discoveries of vitamins A, D, and K and the unraveling of the B family have all come in our time, some of them of practical importance only as newer technics of food processing have made replacement necessary.

Certainly, one of the most notable advances has been in the field of electrolyte metabolism. The repair of acidosis did not prove to be the panacea that was first anticipated, but we are now able to restore far more than the proper concentration of hydrogen ions. Those of us who today handle severe dehydration problems with a routine intravenous drip, who have a chemical laboratory at hand to make microchemical measurements to guide therapy, and who have a variety of therapeutic solutions at one's elbow which now permit some replacement of intracellular as well as a more rational repair of extracellular fluid deficits and distortions, should not forget our debt to the pioneers who made this possible: to Marriott and Schloss, who did much to clarify our ideas of dehydration; to Gamble, who so ably formulated and developed the concept of the body fluid compartments; to Kramer, who more than any other gave us chemical micromethods; and, lastly, to Darrow, who gave us potassium therapy.

The picture of infectious disease has changed unbelievably since World War I. We saw far more infectious disease in those days; we saw severe disease rather than mild, and there were many conditions then fatal for which we now have the effective therapy. The disappearance of many infections is quite as complete as the disappearance of rickets. A pediatric service without a case of congenital syphilis or diphtheria, without a draining empyema, an erysipelas, a retropharyngeal abscess, or a gonococcus vaginitis would have been unthinkable in 1920, but today one can go several years on an active service without encountering any of these. The once omnipresent and often intractable cases of pyelitis are vanishing. We still see scarlet fever, but not the malignant variety; the pneumonias of today are both fewer and milder, and the pulmonary complications of contagious disease now give little trouble.

The "contagious hospital" or "contagious ward" is on the wane. Its beds are difficult to fill. An event that should have had wider publicity was the closing of the Baltimore communicable disease hospital some four years ago. Perhaps there will be more pandemics of influenza. I shall not be rash enough to predict their failure to return, but it is certain, at least, that the thirty-year cycle has been broken. To see recoveries occurring regularly in conditions once invariably fatal — bacterial endocarditis, pyogenic and tuberculous meningitis, miliary tuberculosis, or the survival of an operated tracheoesophageal fistula — events which the young pediatrician of today takes for granted — still gives us older ones a thrill every time it happens.

The coming of chemotherapy was discouraging to the immunologic investigator who saw some of his hard-won therapeutic triumphs —

antimeningococcus, antipneumococcus, and anti-influenza sera and others – displaced overnight. But the immunologist still continues to contribute. We must not forget that the present era has brought us active DPT immunization and gamma globulin; the recent developments in poliomyelitis immunization indicate that the immunologist is very much on the job.

Although many of the diseases with which we struggled yesterday have disappeared or have yielded to newer therapeutic agents, it is true that new diseases have appeared or have been recognized. The newer infections include brucellosis, tularemia, 2 varieties of rat-bite fever, leptospirosis, a number of mycotic infections, some new types of rickettsial infection, several virus diseases, 2 forms of hepatitis, the arthropod-borne encephalitides, cat-scratch fever, and a number of others. New anomalies of metabolism continue to be described – some affecting the synthesis of an important constituent, such as afibrinogenemia and agammaglobulinemia, others affecting absorption or renal excretion, such as congenital alkalosis, Lightwood's syndrome, and Fanconi's syndrome. The reticuloendothelioses have arisen to plague us, as well as cystic fibrosis of the pancreas, erythroblastosis fetalis, and retrolental fibroplasia.

Not only do we have new diseases to keep us busy but also new approaches to old diseases. The pediatric cardiologist has been born and has learned to use new tools effectively, tools that have made undreamed of surgery possible. The endocrinologist, whose only potent products at the beginning of our period were thyroid extract and epinephrine, has given us perhaps his greatest achievement: insulin. Potent pituitary hormones, the sex hormones, and the still glamorous corticoadrenal hormones have altered the course of many diseases.

In the changing pattern of pediatrics, one general trend stands out sharply. We are treating incipient disease rather than advanced disease. This is due in part to better diagnostic tools and in part to a more enlightened public that seeks advice early, a public which supports many social agencies – public health, nursing, school health examinations, and case finding drives to detect chronic disease before it has done irreparable damage, as with the early case of tuberculosis or of heart disease. The pediatricians have been perhaps more public-health minded than any other branch of medicine. They have looked askance at the prophets of doom who foresaw economic disaster and loss of individual liberty in these social (perhaps I should say socialistic) endeavors. On the contrary, they have often taken the lead in bringing them about, and the result has been anything but economic doom for the individual pediatrician. On the contrary, he has profited. Both practicing pediatricians and salaried pediatricians have increased enormously in numbers as the public became aware of the services they could render in the early treatment of disease and in the prevention of disease, for much of pediatrics is now preventive medicine. The immunization procedures belong almost exclusively to the pediatric age. Prevention of accidents is the pediatrician's latest job.

EVOLUTION OF THE MEDICAL CENTER

I have talked so far about some of the changes that occurred in pediatrics in the course of one generation, but I have said nothing of the forces which brought them about or where the new ideas were sparked. Ultimate forces are complex and stimulation is often mutual, making it difficult to decide between the chicken and the egg. But one thing is clear and it is important that we should recognize it – the debt we owe to our medical centers, for, with rare exceptions, they are the sources of the new developments that we have seen. The new science obviously has its home there. The leadership in pediatric thought has come from there.

The medical center is largely an American phenomenon, and, although the pattern was already there, its evolution has taken place in the last thirty-five years. Medical schools, of course, we had, but they were modeled on the European plan – the clinical activities being often widely separated geographically from the preclinical departments and quite as often little influenced by them. Pediatric teaching was typically done in the children's hospital, divorced not only from preclinical but from the other clinical departments as well. It was not an environment to provide either the best medical care or the best teaching or did it foster what we now call clinical investigation. The medical center, a unit in which preclinical and all clinical facilities were in geographic juxtaposition and could stimulate each other, was unique at Johns Hopkins for a quarter of a century. It was greatly strengthened by the introduction of the full-time system in 1912 which made a career of teaching and research possible. At the close of World War I, Johns Hopkins was the only department so organized. Washington University, after one false start, was just starting again under Marriott. But the idea of a medical center – one which contained a full-time academic department of pediatrics – eventually took root, and, when it did so, spread rapidly. Yale and Harvard were

among the first to fall into line. The new medical schools – Duke, Rochester, Vanderbilt, and the University of Chicago – adopted the new type of organization from the start. Reorganization was a somewhat slower process, but the late twenties saw the birth of the Columbia and the Cornell medical centers in New York City and similar developments in many other cities. By the end of that decade, before the political New Deal had been heard of, the New Deal in American Pediatrics was well under way. It has been going strong ever since.

The American pediatric clinic has undergone considerable evolution itself since it first came into being under John Howland. Subspecialties have developed within pediatrics. Howland's philosophy was all against this. The purpose of the clinic, as he saw it, was to train all-around pediatricians, and perhaps that need was paramount at the time when heads of future pediatric departments were urgently needed.

His successor, Park, took a different view. The development of "compleat pediatricians" was not his ideal. He felt that advance in knowledge and better patient care could be achieved by segregation of patients with one disease or one particular group of diseases under one individual with a special interest in the study of that disease or group of diseases. Under Park's aegis, the subspecialties of pediatric cardiology, pediatric endocrinology, pediatric hematology, child psychiatry, and others came into being. Syphilis, tuberculosis, epilepsy, and diabetes were likewise segregated, and special scholars were developed in each of these fields.

This pattern of subspecialization has been widely followed in other clinics and has evolved perhaps to the fullest extent in the Children's Medical Center in Boston. The results have, in my own opinion, fully justified this development, but the mushroom growth and branching out of pediatric departments, exceeding as it has that of other branches of medicine, has caused some concern to medical deans, one of whom remarked: "The trouble with our pediatric departments is that they want to be complete medical schools in themselves."

If the American pediatric clinic has produced the new knowledge and has guided the helm of pediatric endeavor, the Academy of Pediatrics must be given credit for its dissemination and for putting the new knowledge to use. Its phenomenal growth and the quality of its meetings bear witness to that fact.

The picture of the last three decades of pediatrics would not be complete without mention of some of the forces from without that have helped to create what we have today. Creative planning can come to nothing unless the plans are implemented – unless there is money to carry them out. We have been able to get the money – let us admit our debt to a steadily increasing flow of funds from private philanthropic sources, to government funds as well as governmental services to help us do our task, and, finally, to industry. One of the most striking changes I have witnessed is the altered relationship between the pediatrician and the food and pharmaceutic industries. Early in the century, we were just emerging from the patent medicine days. The few firms which were producing standard chemical drugs and a few biologicals were small concerns which conducted no research of their own and made no effort to promote it elsewhere. The purveyor of infant foods was an anathema to the pediatrician, and deservedly so. His efforts were directed to marketing as a complete food a product that was often grossly deficient. The physician who used a proprietary food was regarded by his colleagues in much the same light as one who prescribed a patent medicine.

Times have changed, however. Pharmacologic research, first developed in the universities, has been taken over in large part by the big pharmaceutic houses. The purveyors of biologicals and of foods themselves conduct research on infectious disease and nutritional research of a high order and they have been generous in their support of research in the university clinics, realizing that they have a common interest in furthering scientific knowledge. Abuses and exploitation of the public there are and perhaps always will be, but the ethics of industry as a whole have changed in our time, and, with that, the industrial concerns have become our friends rather than our enemies.

The American child of today is a fortunate human being as compared to his counterpart a generation ago. Studies of prenatal nutrition, done largely by pediatricians, give him a better start at birth. His chance of being born with a malformation is reduced. A vitamin protects him to some extent from hemorrhagic disease of the newborn. His chances of dying within the first year of life are less than one-third of what they were. His parents need not fear an attack of diphtheria. The contagious diseases he acquires will give him relatively little trouble. If one of his parents has tuberculosis, he may get infected but he will not die of miliary tuberculosis or tuberculous meningitis. He will be fed on clean milk and will have better bones and teeth than his predecessor. He will not suffer

from deficiency diseases. If not looked after by a pediatrician, he is likely to be attended by a pediatrically-minded general practitioner. If his mother needs help in child guidance, she can get it. His health and welfare will be looked after in school, even if neglected by his parents. Energetic research is being conducted against all the diseases from which he suffers. If he has the misfortune to acquire a crippling disease, he can get the best of treatment and rehabilitation regardless of its actual cost. Perhaps he will learn to smoke cigarettes and ultimately die of cancer of the lung. That is scarcely the task of the pediatrician to prevent, but, when he reaches his teens, the pediatrician will have done a job. I think we can say with some pride that in our generation American Pediatrics has come of age.

DR. MC QUARRIE'S ACHIEVEMENTS

And now, in closing, I come to the most pleasant part of my task, which is to tell you what part the man we are honoring today has played in the developments I have been talking about. I shall not try to embarrass him by overstatement. The bare truth is enough — it needs no varnishing.

Dr. McQuarrie was one of those whose enthusiasm for the study of disease was kindled early in his career. Perhaps it was the Johns Hopkins atmosphere and perhaps a close exposure to George Whipple that ignited him, but the record shows a stream of productive research dating from his medical school days. At the time he was maturing, biochemistry was just being applied to clinical problems, and the field to which he applied his extraordinary dynamic energy has been, by and large, the field of metabolic diseases and metabolic aspects of disease.

His researches have been on a broad front — protein, fat, and carbohydrate metabolism, mineral and water metabolism, and the endocrine control of metabolism. As new clinical methods appeared, he was prompt in applying them to the study of disease and even devised some himself. It is almost like going through the New Jersey, New York, and New England countryside and finding in one town after another a house where George Washington slept, to go through the metabolic literature of the last three decades. Everywhere, one finds that McQuarrie had been there first. The difference between George Washington and McQuarrie was that Washington only slept there but McQuarrie worked there.

The quantity and the range of his work is prodigious. It is difficult to see how the quality could be maintained in the face of such a large volume of work, but it was. His written papers are models of exposition. It is hard to choose from nearly 150 publications the most significant ones, but I believe his contributions to the relation between water balance and seizures and his observations on the relation between sodium, potassium, and carbohydrate metabolism represent new thinking of a high order. Certainly his observations on idiopathic hypoglycemia — or, as he prefers to call it, hypoglycemosis — warrant naming that condition McQuarrie's disease.

With the recognition that came to McQuarrie for his work came new responsibilities and eventually his present post. Much of his work has had to be carried on with the aid of associates, and it is perhaps the brood of young pediatric eagles that he has raised and inspired that will be his greatest monument. I shall not enumerate them. They are all here today as participants in this program to speak for themselves.

The creation of the Minnesota clinic, developing year by year, incorporating new approaches to the study and treatment of disease as promptly as they appeared on the horizon — and often before they were taken up elsewhere — required a combination of clear vision and energy coupled with diplomacy that is rare indeed. The clinic has been a sphere of influence, a luminous one, an influence throughout the country and beyond, for the local field has not been able to confine the talents of a McQuarrie. It is difficult to think of any significant happening in American pediatrics in recent times in which McQuarrie has not played an active part. He has always willingly given of himself whenever opportunity has arisen.

If I can be permitted to digress for a moment and make a prediction as to the future of American pediatrics, I must confess to regarding it, perhaps incorrectly, in much the same light as did the experts of the World War I era. The evolution of pediatric centers has occurred, and the machinery for war on disease has been built and is operating. The major remaining task seems to be to broadcast the knowledge in this country's and the world's backward areas. If this is so, it would seem to me that McQuarrie has looked into the future and that his most recent activity has been broadcasting of pediatric knowledge into the peripheral areas. Missions to the Orient, participation in international congresses, and, that most ambitious task of all, the editorship of the only pediatric system in English bear witness to this phase of his career.

I think I have talked long enough. In closing, may I congratulate you, Irvine, on four decades well spent in the service of pediatrics and wish you many more years in doing what I know gives you the greatest joy.

Pediatrics, Preventive Pediatrics, and Public Health

HERMAN E. HILLEBOE, M.D., AND
EDWARD R. SCHLESINGER, M.D.

Albany, New York

PREVENTIVE medicine concerns itself not only with the prevention of occurrence of disease and disability but equally so with the prevention of progression of disease and disability. Isolating a tuberculous father from his uninfected children actually prevents the occurrence of infection among the children from the paternal source. Detection of minimal tuberculosis among high-school students by mass roentgenographic examinations provides the opportunity for physicians to prevent the progression of disease because it is discovered in its early and more easily treatable stages.

Problems of preventive medicine become public health problems when they require organized action by the community for their solution. The alert pediatrician is on the lookout at all times for opportunities for preventive services among his patients and their family associates. In one area, preventive medical problems may be the sole concern of the family physician, yet, in another area or at a different time, these same problems may occupy the attention of the public health physician and all the members of his staff. The health department staff and facilities are used to best advantage when they supplement and enhance, rather than replace, the efforts of the family physician in preventive medicine.

Preventive medicine viewed in this broad perspective becomes a synthesis of the skills and experiences of the public health physician and the private physician. Each contributes to the common goals of minimizing the effects of disease and disability and of promoting optimum health and well-being of citizens of all ages in the family and the community.

"Preventive pediatrics" may ring somewhat strangely on the ears, in contrast to "preventive medicine." Preventive pediatrics is the heart's blood of pediatrics, not an appendage grafted onto the body. Because prevention is an inseparable part of pediatric practice today, the term "preventive pediatrics" has never gained wide currency. To some extent, pediatric practice and public health services on the local scene are also inseparable. We may define public health services as organized community health activities carried on for the benefit of the total population or of a segment of the population – in this case, children. Probably a closer working tie exists between private pediatricians and public health workers, in this broad sense, than among any other medical specialists.

These have not been recent developments or minor activities on the periphery of pediatric practice. The writings of Abraham Jacobi, well before the turn of the twentieth century, are replete with discussions of the preventive aspects of pediatrics. This is all the more striking in view of Jacobi's many contributions to pediatric education and the treatment of sick children. Jacobi has been called the pioneer in the bedside teaching of pediatrics in Abt's biographical sketch in Brennemann's *Practice of Pediatrics*,[1] which, as you all know, is edited by Dr. Irvine McQuarrie, the man whom we are honoring.

Jacobi's early contributions to preventive pediatrics take on added significance in the light of subsequent developments. I would like to call attention to one of his addresses, given in 1898, entitled "Some Preventives," in which he ranges over preventive measures in obstetrics, geriatrics (though not called by that name), and other fields as well as in pediatrics.[2] "The object of medical science and art," he stated, "is not confined to removing diseases; it includes also prevention." He so emphasized the importance of sound care of the infant immediately after birth that " . . . . unless there is a vital indication to assist the mother, the baby should be attended to first . . . . " The belief expressed by Jacobi, that asphyxia in the newborn " . . . . may lead to convulsions, paralysis, epilepsy, or idiocy," has only recently been tested on a broad scale. He discusses the preventive role of proper and safe infant feeding, especially the need for

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

adequate "proteid" for growth; the avoidance of overfeeding; and the desirability of keeping young infants well hydrated.

Jacobi's idea of prevention extended beyond the avoidance of initial disease or disability. His concept included the prevention of death in acute febrile diseases. He most certainly included the prevention of recurrent illness or permanent disability, as in the measures he advises for the management of rheumatic fever, or, as he called it, "rheumarthritis." This concept of the prevention of permanent disabilities or deformities is elaborated in his discussion of the treatment of rickets. From what Jacobi suggests, it was apparently the custom to treat only the fairly severe cases of rickets. He asks: "Should we let it alone, and not employ air, and proper food, and cold water, and phosphorus, and iron iodid, and cod-liver oil in mild as in bad cases?" He concludes: "To treat rhachitis in time means to add beauty and brightness and intellectuality to the world."

My only purpose in quoting so extensively from this address of 1898 is to point out how far in the forefront pediatrics has been in the field of prevention. Here, in an address given more than a half a century ago, one of the founding fathers of American pediatrics grappled with the definition and scope of prevention. His ideas were the forerunners of concepts recently developed by the Commission on Chronic Illness and those we follow in the New York State Department of Health in planning and carrying out our public health programs.

Jacobi understood the need for public health education and for the provision of community services for persons who could not obtain them from their own resources. "The community, the State," he says, "has the greatest interest in saving women and babies, if only for economic reasons; for every human being dying early is a loss of labor and means. From that point of view, and as a matter of morality and ethical duty, none should be sacrificed that can be saved."

The continuing interest and leadership of pediatricians in developing preventive services in the broadest sense are epitomized in Dr. Beaven's presidential address before the American Academy of Pediatrics in 1951, when he stated: "It was made clear (before the American Academy of Pediatrics was organized) that pediatricians were now convinced that a society was needed whose principal objective would be not solely to promote social and scientific needs of its members, but which would exist primarily to promote child welfare."[3] This principle has served as a beacon for the activities of the Academy since its formation.

The Academy has striven, through the years, to raise the standards of pediatric practice and of facilities for the care of children. An outstanding example of this has been the work of the Committee on Fetus and Newborn in improving the care of newborn infants in hospital nurseries. The committee has developed a set of authoritative guideposts for newborn care in hospitals. Local pediatricians, working with health departments and hospitals, have made outbreaks of diarrhea of the newborn a rarity in many communities. In several instances, as in our own health department in New York, the development of sanitary code requirements for minimum facilities and services has provided the pediatricians with the leverage required to get hospital boards to make needed changes and to provide sufficient well-trained personnel in the nurseries, which the pediatricians themselves had been unable to attain.

Another indication of the intense interest of pediatrics groups in meeting the total health needs of children is the large number of pediatricians who have entered the field of public health. This is only an impression on my part, since I do not know of any relevant statistics on the subject, but I would surmise that the proportion of pediatricians in public and private health agencies far exceeds that of any other medical specialty. Many persons in public health who have had pediatric training have invaded broader fields than maternal and child-health alone. We are proud to number ourselves among those trained in pediatrics who have gone into public health as a means of applying, on as broad a scale as possible, the principles and practices taught during our years of postgraduate training.

The trend toward integration of pediatric practice, preventive pediatrics, and public health is still continuing. When we accept preventive pediatrics as an essential part of both the private practice of pediatrics and of many public health services, we can see that a strong 2-way relationship exists. On the one hand, many public health activities are of direct or indirect benefit to pediatricians in private practice and to their youthful charges. Public health personnel look to the pediatricians for help in reaching children in the community under private care. In addition, pediatricians, individually and as a group, can help in the development and full use of organized community efforts to promote child health, normal mental and physical growth, and family well-being.

EFFECTS OF PUBLIC HEALTH ON PEDIATRIC PRACTICE

Let us examine some of the ways in which organized community health activities affect the private practice of pediatrics. One of the first principles of public health should be stated at this point, namely, that public health seeks to have as many persons as possible assume responsibility for obtaining through their own resources needed health services. Only when families cannot do this for their children due to financial or other overriding reasons should the community step in to assist. In other words, organized community health services for children are intended to supplement and reinforce, rather than replace, private pediatric services.

Pediatricians in private practice, therefore, have much to gain, both professionally and economically, from the development of adequate community health services for children. Community health activities have promoted private pediatric care and continue to do so. Health education activities of health departments and voluntary agencies, for example, have emphasized the importance of regular health supervision of children from birth through adolescence. The value of continued care during periods of apparent health, as well as during illness, has been constantly repeated through all available media of public education. Probably the most effective media have been the booklets for parents on prenatal, infant, and child care. Millions of copies of these have been issued over the past several decades.

These general methods of public education have been strengthened by the specific activities of public health nurses who visit homes in the community not otherwise reached in which health problems of countless varieties are found. In addition, child health conferences, or well-child clinics, increase the demand for child health supervision by private pediatricians. Most health departments today consider child health conferences primarily as educational tools, demonstrating to the community the value of continued health supervision for children. Similarly, community health organizations have hammered away at the need for childhood immunizations against diphtheria, smallpox, whooping cough, and tetanus; others may soon be added to the list. This campaign has certainly been responsible for at least part of the present almost universal acceptance by the public of such immunizations on a routine basis.

Even when the public health agencies make no special effort to emphasize the educational aspects of their activities, the net effect is to increase the amount of service requested of pediatricians. This has been recognized by pediatricians in the American Academy of Pediatrics' study of child health services, which stated: "It has been demonstrated time and time again that when public health services are brought into a community, there is a concomitant increase in the demand for private care. As the community learns the value of diphtheria immunization, more patients request it of their own physicians."[4]

Professionally, pediatricians have much to gain from well-developed public health services in their communities. In all the activities of health departments, for example, emphasis is placed upon the early discovery of disease or disability and upon follow-up to see that the child is brought under the care of the family physician or pediatrician. Public health nurses, in particular, through many contacts and friendly associations in the areas they serve, learn of children who are not receiving medical care. In home visits, they may learn of untended illness or notice some indication of poor health in several young members of the family. In such instances, the well-trained public health nurse will refer the problem to the family physician or pediatrician and be guided by his advice as to further steps to be taken.

Through these combined efforts of public health personnel, the pediatrician sees many patients early in the course of illnesses and, in many instances, is thereby able to provide more effective treatment at less cost to the patient. Routine follow-up of such conditions as poliomyelitis or hemolytic streptococcal infections may disclose complications or disabilities not evident during the acute stage of the disease. If the family does not return to the physician who provided care during the acute phase of the illness, these diseases and disabilities too frequently progress to severe involvement.

In other respects, too, the availability of public health nursing services enables the pediatrician to provide better care for his patients, oftentimes at less cost. When a pediatrician has a patient with a condition that requires periodic check-ups, he usually hesitates, for ethical reasons, to communicate with the family directly when the patient fails to return. The ethical problem does not intrude if he requests the local health department to follow up and endeavor to have the patient brought back for care. Also, there are times when children can be given care in the home rather than in the hospital if someone in the family can be taught the essentials of home nursing and similar measures. This is

one of the valuable services the public health nurse provides. Such services at home are assuming increasing importance with more widespread understanding of the possible emotional trauma associated with hospitalization of children. Greater emphasis is given to the desirability of providing care in the home when the condition of the child allows or when diagnostic and therapeutic procedures obtainable only in the hospital are not needed.

PEDIATRICIAN'S ROLE IN PUBLIC HEALTH

The aforementioned are some of the ways in which community health services can be of help to the pediatrician and the children under his care. In what ways can the pediatrician help insure that the children in his community receive the benefit of modern preventive services? The first responsibility of the pediatrician is, of course, to the children under his private care. The well-trained pediatrician is expected to have a thorough grounding in the growth and development of children, in their interrelated physical, emotional, and social phases, and in the principles of modern nutrition and prevention of specific diseases. The community looks to him to apply these principles as part of his care. There can be no substitute approaching in effectiveness the intimate relationship of a pediatrician to a family through sickness and health. When families cannot obtain such service out of their own financial resources or when pediatricians do not accept their responsibilities in providing such care, the organized community health program will try to supplement these services.

That pediatricians as a group are cognizant of their responsibilities in prevention is well known to the community at large. An indication of this is the fact that special immunization clinics have been curtailed drastically or eliminated entirely in many communities. This is because immunization against diphtheria, tetanus, whooping cough, and smallpox has become so much a routine part of private practice in these communities that there is no longer need for special clinics. I venture to say that, should the present or some other poliomyelitis vaccine prove successful in warding off or mitigating the effects of the disease, its use will become a routine part of pediatric practice within a few years.

When some phase of preventive child care comes to the fore in a community, those civic leaders involved in planning often call in first the practicing pediatricians to insure adequate attention to the preventive services under consideration. The best and most recent example of this is the growing interest in many areas in the promotion of child safety. Through the excellent work of Dietrich[5] and others, it has been amply demonstrated that the prevention of disabling or fatal accidents in infancy and early childhood should be undertaken as part of general child health programs. The principles of anticipatory guidance, developed for other phases of child growth and development, are equally applicable to the prevention of childhood accidents. By preparation for each successive phase of the child's development, parents can be helped to take the needed steps to protect the child against the particular hazards of each age and to teach the child increasing responsibility for his own safety. When child safety programs have been initiated, a very important phase involves reaching individual parents as an essential part of preventive services provided by pediatricians.

In addition to giving optimum pediatric care to the children in his private practice, the pediatrician has other responsibilities in helping to promote better health for all the children in his community through organized child health activities. These public measures fall roughly into 2 broad categories. The first of these consists of activities which affect the entire community or, at least, a large segment of it. Included are such measures as the provision of safe water and milk supplies, the elimination of traffic and other accident hazards in public places, and the fluoridation of public water supplies to reduce dental caries. At first glance, the private practice of pediatrics would seem to have little direct connection with these matters. However, the practicing pediatrician certainly wants his patients to have the benefit of these preventive measures. Through the force of his personal and professional prestige in the community, he can make a valuable contribution in helping to bring relatively new preventive measures, such as water fluoridation, to his community and to insure maintenance of these measures once they are started.

The second major aspect of the community child health program is the provision of individual services which are beyond the financial ability of the families to obtain or which are not otherwise available in the community. These are many, and the patterns of services vary in different communities, depending upon local needs and resources. Public health nursing services are almost universally available where an organized public health program exists. Activities of communicable disease control continue to have an important place. Child health conferences, school

health programs, consultation services of various types, specialized care, and rehabilitation services for handicapped children form part of a complex pattern of health services in this country. Some of these services may be provided by the health department, others by voluntary health agencies, still others by special hospitals. Some may have been developed as a result of a carefully worked-out plan based on analysis of community needs; others may have come into being as a result of public demand. Detailed analysis of the problem may have led to legislation mandating the provision of such services by the health department or to financing and provision of the services by voluntary health agencies.

Whatever the impetus for the development of these health services, the practicing pediatrician again bears certain responsibilities and can make definite contributions to the establishment of the best type of service. By taking part in the initial discussions of the need for the services, he can help guide these services into the most useful channels. By actual participation in several phases of these services, he can provide the quality of pediatric care needed to insure the effective expenditure of funds and efforts. By knowing of available services in the community, he can make prompt use of these services for patients in his own practice as the need arises. There are undoubtedly many families in every pediatrician's practice who can pay for ordinary medical care but whose relatively meager resources are exhausted in the face of prolonged hospitalization or disabilities requiring long-term rehabilitative services. Children with severe hearing loss or cerebral palsy, for example, should have the benefit of recent advances in rehabilitative technics when these are obtainable in the community. Even if the family can pay in part or in full for these expensive services, the pediatrician is often the person who must refer the child for such care. When the family cannot afford these services, the pediatrician should know where to turn for assistance for the family.

In many phases of the community health program, the knowledge and full cooperation of the family pediatrician is essential to the success of the program. A good example of this is school health services. These services do not have good repute in many communities because they have consisted, in large measure, of unrewarding, cursory medical inspections on an annual basis, without regard to whether or not the child had a family physician who might have performed the examination in the first place. There is, increasingly, a professional opinion that the inspection type of program is of little value. Communities have been supplanting this with a program based on less frequent but more careful medical examinations, including adequate screening tests for vision and hearing and sufficient time for medical histories and interviews with the parents. More careful interim observation of school children, with prompt examinations and referrals to family physician or pediatrician in the event of any physical or emotional deviations, is needed to modernize school health services. Basic to this program is the encouragement of more family responsibility in having these examinations performed by the family pediatrician, with recommendations to the school if modification of the school routine is indicated to meet specific health needs of the child.

Pediatricians can be most helpful in promoting modern school health services in the first instance. Once such a program has been instituted, its continued success is dependent in large measure on the adequacy of the information submitted by the pediatrician to the school and on the thought he gives to preparing recommendations to the school. The natural antipathy of all physicians to the chore of completing report forms is a real obstacle to the maintenance of good school health services. The pediatrician must learn to look upon the completion of the required forms as one of the essential means of providing basic data for the promotion of better health among children.

The pediatrician may also be of great help by serving as a listening post in the community and, when indicated, by calling attention to health problems. This is certainly the case in communicable diseases which tend to occur more frequently in childhood. These diseases are usually reportable by law, and the pediatrician has this responsibility. But what about other health problems of a noncommunicable nature? One such condition that comes to mind is methemoglobinemia due to drinking well water containing relatively high concentrations of nitrates. This is, as you well know, a condition mainly affecting young infants whose feedings are prepared with water from such sources. In some areas, pediatricians were the first to suspect this diagnosis. They called the matter to the attention of the local health departments, which were then able to investigate the problem and take the necessary measures to prevent additional cases.

The occurrence of many cases of nutritional anemia and other nutritional deficiency states

has likewise been called to the attention of the local health departments by pediatricians and has served as a basis for public health education and other corrective measures. A study of congenital malformations received a strong impetus as a result of the observation of the occurrence of congenital malformations following maternal rubella in Australia.

PUBLIC HEALTH AND RESEARCH

Mention should also be made of the close relationships between clinical pediatrics and public health in the field of research. Two recent examples may be cited, one relating to retrolental fibroplasia and the other to the diagnosis of measles in the preeruptive stage. Seldom has a health problem involving relatively small numbers of persons excited so much interest among professional circles and the general public as has retrolental fibroplasia. Epidemiologic studies, including those carried out by the New York State Department of Health, helped define the extent and distribution of the problem. Clinical studies carried forward by pediatricians and ophthalmologists at a number of medical centers clarified the pathogenesis. The cooperative clinical study sponsored by the National Institute of Neurological Diseases and Blindness and the English studies promise to provide a definitive answer on the role of oxygen in this condition. These studies should establish a firm basis for the proper management of the premature infant to avoid development of this condition and subsequent visual impairment or blindness.

Research contributions important to pediatric practice come out of public health laboratories in a continuous stream. An observation by Tompkins and Macauley in the Division of Laboratories and Research of the New York State Department of Health, in conjunction with the Department of Pediatrics at the Albany Medical College, is a recent example.[6] Following a lead from postmortem studies of the bronchial mucosa in a case of measles, Tompkins and Macauley found what appeared to be pathognomonic epithelial giant cells from the nasal mucous membrane in the prodromal stage of measles up to five days before the appearance of the exanthem. The cells are readily demonstrated in the glairy mucus obtained by a glass-rod applicator, or by direct swab of the nasal mucosa. This new and single technic may prove to be useful to pediatricians in advising parents of proper action among exposed contacts in the family or hospital.

CONCLUSION

These brief remarks, I hope, have shown the close community of interest between the private pediatrician and health workers in the official and voluntary health agencies. Current developments in pediatrics and public health are such that we can look forward to an increasing emphasis upon the role of prevention in private practice. There is every reason to expect an increasing assumption of pediatric responsibility for the integration of preventive technics into private practice and a greater understanding and use by the practicing pediatrician of community health services for children.

The benefits of preventive pediatrics and public health accrue not only to the growth and development of children but also to their families' health and the well-being of the community as a whole.

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Experiences with Hemolytic Disease of the Newborn

ERLING PLATOU, M.D.
Minneapolis, Minnesota

In HEMOLYTIC DISEASE of the newborn, it is now well established that inherited fetal antigen different from that of the mother causes the formation of antibodies in the mother's blood or accentuates those already present if she has been sensitized by previous injections of incompatible blood. The antibodies thus produced may remain harmless unless they traverse the placental barrier and produce a specific reaction in utero or in the neonatal period. They may cause agglutination and hemolysis of fetal red cells and result in fetal hydrops and stillbirth or hemolytic icterus with varying degrees of anemia. The antigens thus far implicated in such a process are A, B, C (Rh′) D (Rh_0) E (Rh″) and several very rare subtypes[1,2] (table 1).

TABLE 1
BLOOD GROUP ANTIGENS THAT MAY CAUSE ERYTHROBLASTOSIS FETALIS

AB	A-B-O "family"
D (="Rh"	Rh "family"
CC^wc	
Ee	
Kk	Kell "family"
M	M-N-S "family"
Ss	
Jk^a	Kidd "family"
Fy^a	Duffy "family"

Six of the 9 known blood group families are shown. The others (Lewis, Lutheran, and p) do not cause clinical problems. A_2, O, N, Jk^b, and Fy^b are known, but have not been reported as causing erythrohlastosis. The variant of D known as Du not included above, may cause erythroblastosis. D is the antigen Rh_0 of Wiener et al., C is rh′, C^w is rh^w, c is hr′, E is rh″, e is hr″.

Group A and B antigens have recently been shown to be of greater importance than once thought.[3,4,14] The original Rh factor, designated by Wiener as Rh^0 and by Race and Fisher as D, occurs in 85 per cent of white people. Rh′ or C occurs in 30 per cent of white people. Some individuals, therefore, have been shown to have 1 factor only, some 2 or 3, and some none. The incidence and alternate terminology are presented in Table 2 (from Wiener, Fisher and Race).[1]

Fisher[5] advanced the theory that, if an agglutinogen lacks any of the Rh factors, Rh^0 (D), Rh′ (C), and Rh″ (E), it has in its place a contrasting factor Hr^0 (d), Hr′ (c), and Hr″ (c), respectivcly. Therefore, rh contains all 3 Hr factors and would react to all 3 anti-Hr antisera. Rh′ (C) contains Hr^0 (d) and Hr″ (e) and would react to anti Hr^0 (d) and anti Hr″ (e) sera, and so forth. Therefore, if a patient is homozygous, she will be Hr negative. The Hr factors are relatively weak antigens and account for only 2 per cent of cases of erythroblastosis, most all of which are Hr′ or c.

Serologic tests which led to the discovery of the Rhesus factor in humans clarified our understanding of the pathogenesis of hemolytic disease of the newborn. Although the incidence of Rh negative women is much less in most other races, it has been shown to be 15 per cent in the white race. Because the father may be heterozygous or because the familial constitutional potential of the mother for antibody production is limited or because of unknown reasons, the percentage chance of serious consequences of Rh incompatibility is relatively small. Unless a mother has been previously sensitized by blood injections or unless there is A-B-O incompatibility, the first pregnancy usually results in a normal Rh positive baby. Erythroblastosis occurs with subsequent pregnancies, and, in some families, a progressive increase in severity is apt to occur with successive pregnancies.

Most intragroup cases can be positively diagnosed by the use of anti Rh_0 or anti D serum.

TABLE 2
FREQUENCY OF THE 8 Rh CHROMOSOMES IN WHITE POPULATION

Alternate terminologies		
Wiener	*Fisher-Race*	*Per cent*
R^1	DCe	41.1
r	dce	36.6
R^2	DcE	17.0
R^0	Dce	3.3
r′	dCe	1.4
r″	dcE	0.5
r^z	DCE	.1
r^y	dCE	.01

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

In a typical case, the red cells of the father and infant are Rh positive (D) and those of the mother are Rh negative (d). Specific antibodies are found in the mother's serum and on the surface of the baby's red cells. In about 5 per cent of cases, the mother is found to be Rh^0 positive, but incompatibility with respect to a subtype such as Rh' (E) or any of 12 other rare antigens, (table 1), can be demonstrated with appropriate serologic technics. Probably 95 per cent of all cases of severe hemolytic disease are due to Rh incompatibilities; 2 per cent are due to Hr (cde) incompatibilities, and perhaps 3 per cent to A-B-O incompatibilities. In the mother not previously exposed to Rh positive blood, 1 or even more normal Rh positive babies may be born, but, since in man, only a single layer of syncytial cells separates the vessels of the expanding placental villi from the maternal sinuses, it is understandable that antigenic fetal red cells may easily gain entrance into the maternal circulation and initiate or augment isoimmunization. It has been estimated that as little as 0.03 cc. of fetal blood will bring about isoimmunization, and yet, in full-term pregnancies, the incidence of hemolytic disease is only about 1 in 150 such cases.

Prior to 1944, saline suspensions of cells were employed for maternal agglutination tests and only one-third of serums of Rh negative mothers whose babies had hemolytic disease contained Rh antibodies. Diamond and Abelson,[6] through the introduction of the "albumin" slide agglutination test, showed that protein was a necessary ingredient of the medium for testing. Race[7] and Wiener[8] both showed that Rh receptors on the cells were coated by another antibody, so that the saline reaction was "blocked." These antibodies released by plasma and heat were, therefore, termed "incomplete" or "blocking" antibodies. Coombs and associates[9] then announced the important discovery that the coating with blocking antibody could be detected by a positive reaction. They showed that sensitized red cells, after washing for removal of soluble protein, can be agglutinated by rabbit antiserum prepared against human globulin. Cells with maternal antibody on their surface are agglutinated while normal cells are not affected.

Formerly hemolytic disease due to anti A and anti B factors was thought to be rare or nonexistent, and that high titers against heterologous blood group antigens were without significance. The large molecular size of the relatively potent A and B antigens was believed to prevent their entry into the maternal circulation. More recently the important discovery has been made that mild hemolytic disease due to A and B factors is not rare,[1,10–14] and that it differs in some rather characteristic ways from that due to the Rh factors. Although some doubt was cast on the existence of A-B-O type of erythroblastosis fetalis for a time, the fact that survival studies in which group O blood survived normally in affected infants, while red cells incompatible with the mother's serum disappeared rapidly, was rather conclusive proof of its occurrence.[11]

If the parents belong to the same blood group or the dominant A or B factor is found in the mother's blood, there is compatibility. If, however, it is present in the father and not in the mother, there is the potentiality of hemolytic disease. Of all white matings in the United States, 35 per cent are A B-O incompatible, but, since most are heterozygous, incompatibility of infant cells with maternal serum occurs in only 26 per cent of cases. The frequency of hemolytic disease attributable to this cause is reported as between 3 and 20 per cent of all cases depending on the selective nature of the material. The diagnosis of hemolytic disease due to A and B factors cannot be predicted but must be made on the infant after birth. The clinical and pathologic features closely parallel those due to Rh incompatibility. Unlike these, however, the disease frequently occurs in the first pregnancy and the diagnosis is more difficult. Early jaundice and a positive direct antiglobulin Coombs' test on the infant's red cells is proof of the diagnosis of hemolytic disease. While the red cells may give a negative or weak test in the A B-O disease, cord specimens are more apt to give a positive test, and some laboratories now use the "double Coombs' test" which augments the sensitivity of the conventional test. In the latter, after a negative Coombs' test, the cells are washed three more times and another drop of antiglobulin rabbit serum is added. Agglutination signifies that the cells are sensitized with human antibody. High maternal anti-A and anti-B titers are not of prognostic value. They may occur with normal infants, although the rise in the case of an affected patient will usually be more striking, especially in instances when the baby is an A-B secretor.

The diagnosis rests principally on the findings in the infant who becomes jaundiced *soon after birth*, although usually later than the Rh cases. In the premature, who is especially susceptible to kernicterus, this may be mild and easily confused with physiologic icterus, which can be diagnosed by exclusion only. In fact, Zuelzer and Kaplan[11] think that A-B-O evidence may be so mild that it should often be termed icterus prae-

cox (Halbrecht). As in the Rh type of disease, anemia, bilirubinemia, reticulocytosis, and normoblastemia often occur and can be detected in cord blood. However, instead of macrocytosis, as seen in the Rh incompatibility disease, the blood smear usually reveals microspherocytosis resembling that present in congenital spherocytic anemia. There is also increased erythrocyte fragility. Fortunately, many cases are mild and require no treatment or merely a packed-cell transfusion. The more severe cases should be subjected to exchange transfusion, according to the same criteria as the Rh cases. Group O blood with A and B substance added should be employed.

Whereas almost all cases of hemolytic disease of the newborn can be detected by A, B, C, D, and E sera that fulfill the requirements of the National Institute of Health, it must be realized that there are unusual patients in whom these tests prove negative. Detailed studies to detect such antibodies as Du, Kell, and other factors must be carried out in especially equipped laboratories by personnel with wide experience in serology.

The prognosis in erythroblastosis has been shown to depend upon antibody potential which in some families is very low, whereas in others it is very high — a constitutional factor apparently predetermines the outcome. Similar reports by Potter,[12] Allen and associates,[13] and others seem to confirm this finding. In families whose first erythroblastotic infant lives, there are many more living babies subsequently; whereas, in families whose first baby dies, most subsequent babies are stillborn or die soon after birth.[14] If sensitization is not detected early in pregnancy, a good prognosis for survival is usual, even in those cases where antibodies appear later. The frequency of hemolytic disease due to Rh or D factor in the susceptible group, in general, is only 1 in 20. Its frequency is about 1 in 42 for its first occurrence in the second pregnancy of the Rh sensitized types, and 1 in 12 in the fifth pregnancy. The frequency of heterozygosity of fathers and the trend toward small families explain the relative infrequency of erythroblastosis. In Negroes, among whom only 5 per cent of mothers are Rh negative, and in American Indians, among whom only 1 per cent are Rh negative, the disease is extremely rare. In the current generation of pregnant women, the incidence of erythroblastosis is greater, due probably to previous sensitization resulting from the frequent use of injections of blood not matched with respect to the Rh factor.

Hemolytic disease of the fetus is seen in its worst form in fetal hydrops, or stillbirth. In the latter, maceration of tissue makes histologic findings valueless, and the diagnosis must rest on serologic grounds except for the finding of young erythroblasts in the pulmonary capillaries. Generalized edema differentiates it somewhat from the fat baby of a diabetic mother, which also exhibits hypertrophy of the islands of Langerhans. Erythroblastosis fetalis must, of course, be differentiated from the edema of congenital heart, congenital kidney, or gastrointestinal tract anomalies. This differentiation may be difficult in stillborns. If the erythroblastotic infant is born alive, delivery may be difficult because of the baby's large size. The hemoglobin, erythrocytes, and serum proteins are markedly diminished. There is generalized edema, ascites, and hepatosplenomegaly. Tissue pallor is more striking than jaundice, bile pigments having been excreted through the placental circulation. Extramedullary hemopoiesis is found in the liver, kidneys, spleen, and intestinal mucosa. Although the liver may not be a good organ for examination because of normal erythropoiesis here before birth, hemosiderosis, fibrosis, and biliary obstruction can often be seen. Potter believes that the lung is the most useful organ for examination because of the relatively small amount of autolysis. In spite of the fact that there is no evidence of red-cell formation, rather characteristic large primitive red cells are present which tend to obstruct the pulmonary capillaries. In the large vessels many immature cells can be seen in the clots. In the premature infant more widespread erythropoietic tissue is found. Potter[14] and Zuelzer[14] have reported little or no erythrophagocytosis in early cases, but a large amount in those who live two or three days. The placenta is usually thickened and edematous and has hydropic villi. The fetal surface and the cord may show yellowish discoloration. Potter[14] has reported the persistence of Langerhans' cells inside the syncytium covering the chorionic villi. Figures 1 and 2 illustrate some of the changes in the lung and liver seen in a fatal case in a premature infant.

The vast majority of neonatal deaths are due to icterus gravis, which in the newborn may be associated with cardiac failure, as indicated by high venous pressure and pulmonary hemorrhage and edema. In an infant who survives this stage, kernicterus often develops and the baby dies or has permanent neurologic sequelae. These cases are characterized by jaundice of the skin and of all organs, splenomegaly, hyperbilirubinemia, and staining of brain tissue, especially in the nuclear masses (figure 3). Death in the

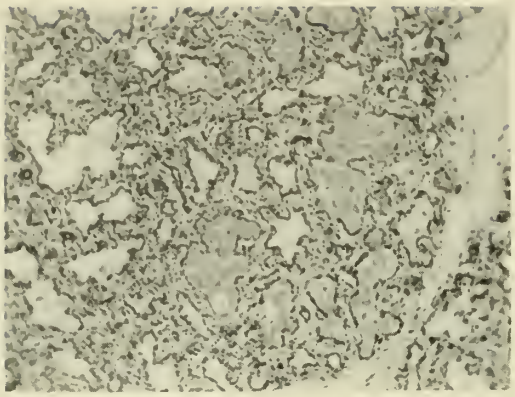

Fig. 1. Section from lung of a premature infant with erythrohlastosis.

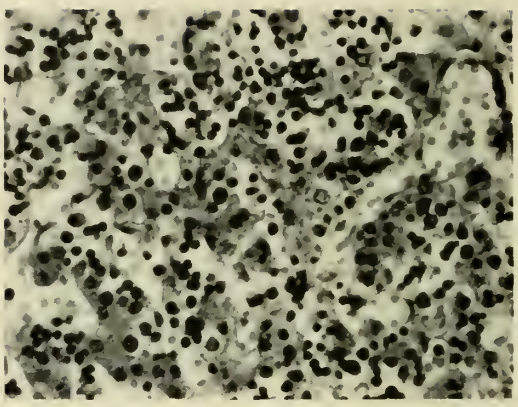

Fig. 2. Liver from a premature infant with erythroblastosis.

latter cases is due to impaired liver function and kernicterus and not to anemia. Petechiae occur on the surface of the liver, in the lungs, and even about the brain.

Among infants born alive, the most serious complication of hemolytic disease is *kernicterus*, which is found in most babies who die after the first day. This complication is believed to be a postnatal development,[14,27] since it is not seen in stillborn infants. Furthermore, symptoms associated with staining in the nuclei and other parts of the brain and cord do not develop until shortly before death, nor are any changes due to icterus usually found in infants who die in the first three days. These facts and the lowered incidence of kernicterus in babies, who have had replacement transfusions, have been offered as evidence to support the concept that kernicterus occurs postnatally.

Although kernicterus is now generally believed to be caused by bilirubin[15] or a closely allied chemical, the intimate mechanism of nerve injury involved in its pathogenesis has not been revealed. Injury from hypoxia or trauma is believed by some authors to antedate the staining. Anemia, fixed antibodies, and liver toxins have been fairly well excluded as causes.

In a review of autopsy material, Becker and Vogel[16] determined that, although there is a focal distribution of yellow pigment in the nuclear masses as early as the second day of life, not until after this time can histologic evidence of nerve cell degeneration and glial proliferation be found. Day[17] has demonstrated by animal experiments that brain tissue must be damaged before it readily takes a vital dye such as bilirubin. The nature of the damage is apparently immaterial since mechanical injury, hypoxia, hypoglycemia, and x-radiation are equally effective in the experimental animals. Other experiments have shown that when a young animal is flooded with dye, staining of the brain in these immature animals occurs at lower concentrations than in adult animals.[18] However, the fact remains that, although certain animals are capable of developing erythroblastosis, they never seem to suffer from kernicterus. Staining of the normal adult rat brain could not be demonstrated by Day until serum levels of 60 to 70-mg. per cent were reached. Such animals may convulse and die, but their brain contains no intracellular pigment. Induced hypoglycemia under these conditions results in histologic changes resembling human kernicterus.

According to Najjar,[19] bile tends to be absorbed on surfaces. He found that most of the pigment in the serum, as a result of hemolytic jaundice, is unmodified, indirect in its reaction, and similar in spectrophotometric pattern to

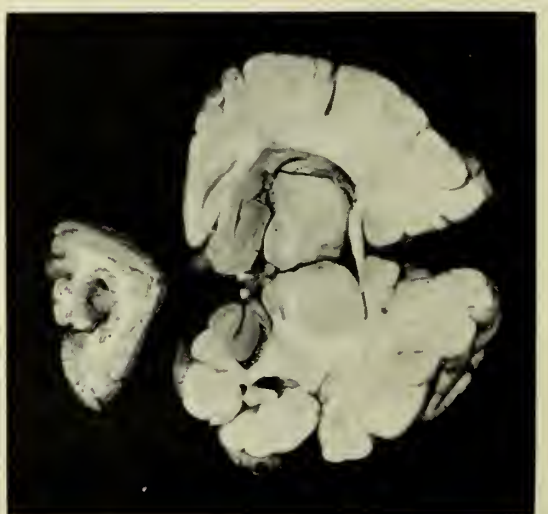

Fig. 3. Staining of brain tissue by jaundice, particularly in nuclear masses.

globulin. Hsia and associates[20] cite cases in which the serum bilirubin was 40-mg. per cent or more, but in which the indirect fraction never exceeded 25-mg. per cent. The fact that none of these cases developed kernicterus suggests that the indirect fraction is more specific. Adams[14] has called attention to the fact that the level of serum bilirubin in hemolytic disease of the newborn exceeds the level that would be expected from hemolysis alone and suspects that liver dysfunction or some other end product of hemolysis may play an important role.

Najjar[19] has demonstrated that brain tissue depends on cytochrome systems containing heme for tissue respiration and suggests that, since bilirubin is similar to heme, it may compete for the protein linkages in the cytochrome systems and render them inactive for oxygen transfer. Day found that bilirubin in concentrations greater than 20 to 25-mg. per cent depressed the respiration of the rat brain by 25 per cent in vitro. Cytochrome C reverses this inhibition. Methylene blue also accomplishes this reversal but at a much slower rate.

These data all suggest that the cellular damage present in kernicterus is related to the indirect reacting bilirubin and that bilirubin must be incriminated as a toxic agent rather than vindicated as being a stain only. Although further investigation is necessary finally to establish this mechanism, clinical experience supports the general implication that hyperbilirubinemia is the toxic factor.

It is now established that while anemia is the chief danger in fetal life and complications of anemia cause almost half of the deaths from erythroblastosis, kernicterus is a postpartum development and bilirubin is the pigment found in the damaged brain cells.[14,19] Controlled studies by Mollison and Walker[21] revealed the incidence of kernicterus to be 5 times greater in infants treated by early simple transfusion than in those treated by exchange transfusion. This would suggest that persistent elevation of the serum bilirubin above a critical level is responsible for the development of kernicterus.

Since the introduction of modern serologic technics, 179 cases of hemolytic disease of the newborn have been treated at the Northwestern and the University of Minnesota hospitals in Minneapolis. Table 3 demonstrates the pronounced difference in average peak serum bilirubin levels in the 2 groups of patients in our study. In those in whom kernicterus did not develop, an average peak serum bilirubin level of only 11.01-mg. per cent was found, while in those in whom kernicterus did develop, the average peak serum bilirubin level was 25.3-mg. per cent.

TABLE 3
AVERAGE PEAK SERUM BILIRUBIN LEVELS 179 CASES (NORTHWESTERN AND UNIVERSITY OF MINNESOTA HOSPITALS, MINNEAPOLIS, MINNESOTA)

	Serum bilirubin
Nonkernicterus	11.01-mg. %
Kernicterus	25.3 -mg. %

Hemolytic disease of the newborn was usually not manifest, and the diagnosis and appraisal of prognosis were largely dependent upon laboratory procedures and the clinical history. Multiparity, previous bad maternal history — live or lost babies with erythroblastosis fetalis — homozygosity of the father as determined by Hr tests, persistently elevated, suddenly elevated, or increased "blocking" antibody titer, followed by a rapid drop, jaundice occurring during the first twenty-four or forty-eight hours and a positive Coombs' test were all found to be important signs, especially when associated with rising bilirubin levels. Anemia with reticulocytosis and leukocytosis was significant, whereas normoblastemia was inconstant and was found in some other disturbances of the newborn as well.

Most severely affected babies were pale, edematous, and lacking in muscular tone. They were often resuscitated with difficulty and the spleen and liver were enlarged. Petechiae, ecchymoses, dyspnea, cyanosis, and circulatory failure became evident. Brain damage was suggested by stupor, twitchings, or convulsions. Cord blood hemoglobin, which Mollison and others[21,22] have shown to average 13.6-gm. per cent in the normal infant, was often under 10-gm. per cent with a red blood cell count frequently under 3,000,000 per cubic millimeter in hemolytic disease. Anemia was of the macrocytic type, unless the cause was A-B-O incompatibility, in which case microspherocytosis occurred. Bilirubin, which is but rarely over 3 mg. per 100 cc. of blood in the normal full-term infant or at most 5-mg. per cent on the fifth postpartum day before receding, was often elevated in some cases of hemolytic disease. Due to excretion of the pigment through the placenta blood, bilirubin values did not rise until after the cord was cut; so that repeated estimations were found to be important. Increases of 1 mg. per hour are ominous and, if they reach beyond 20 or 30 mg. per 100 cc., nuclear staining is very likely to occur. Oxalated or heparinized cord blood was submitted to the laboratory when possible, to obtain a complete blood count, blood grouping, Rh typing, reticulocyte count, bilirubin and direct antihuman

globulin (Coombs' test). If the Coombs' test was positive, the diagnosis of erythroblastosis fetalis was essentially established while, if the test was negative, it usually excluded the cause as Rh-Hr incompatibility but not A B-O difficulty.

Of all tests, hemoglobin concentration was generally regarded as the best index of severity of the process, although a rising bilirubin level after birth seemed equally significant to us. The urine was not of diagnostic help as a rule, although albumin and pigments were occasionally excessive. All but 1 infant in our series born with universal hydrops succumbed or were stillborn.

The clinical picture of anemia, jaundice, and edema had to be differentiated from other conditions that often present these findings. Included among this group and sometimes differentiated with difficulty were such conditions as hemolytic and nonhemolytic congenital familial jaundice, congenital syphilis, toxoplasmosis, congenital thrombocytopenic purpura, leukemia, asphyxia neonatorum and physiologic jaundice, the latter especially when present in premature infants. The laboratory was invaluable in this differentiation.

Although it is true that saline agglutinins in the mother sometimes correlate poorly with severity of the hemolytic process in the infant, the same cannot be said with respect to incomplete or blocking antibodies. Infants born of mothers with blocking antibody titers of over 1 to 32 generally were severely afflicted.

At Northwestern Hospital in Minneapolis, among 110 cases of hemolytic disease of newborns, 26 patients died. The peak saline antibody titer of the mothers of these babies averaged 257.6. Of 84 patients with disease considered severe enough to warrant exchange or interval transfusions, but who survived, the average peak saline antibody titre was 110. The average blocking antibody peak was 64 in the fatal cases and 32 in the recovered cases (table 4).

Although there were a few outstanding examples of high titers with mild disease and low titers with severe disease, high saline and especially blocking titers by the albumin plasma technic usually were associated with cases that had a greater degree of morbidity and mortality. Women in whom a history of incompatible blood injection or transfusion could be elicited, almost invariably gave birth to severely afflicted babies regardless of their antibody titers. Likewise, most infants born of mothers with a moderate but persistent elevation of titer during pregnancy were victims of hemolytic disease, although notable exceptions did occur. Wiener and associates[23] now regard titers in excess of 1:8 by the albumin-plasma method as indicating a potentially severe process.

The earlier attempts at induction of labor before thirty-seven weeks resulted in more babies born alive, but this was offset by deaths from the hazards of prematurity and kernicterus to which the premature is so susceptible. Early delivery by section in the first cases treated showed poor results, as indicated in table 5, and was abandoned.

Induction of labor at thirty-eight weeks does seem rational in patients whose previously moderate titers have risen rapidly by the thirty-sixth week, although cesarean section should be avoided, if possible.

Reports from the literature thus far indicate that most attempts to neutralize antibodies with Rh hapten have failed to alter the disease in the fetus.[23,24] Among 32 cases treated diligently with Rh hapten at the University of Minnesota and Northwestern hospitals in Minneapolis during the past eight years, the incidence of kernicterus was 15.6 per cent, while in a control series of 65 cases who received no Rh hapten, kernicterus occurred in 18.4 per cent (table 6).

The mortality in the group treated with Rh hapten at the University Hospital (50 per cent of whom were also exchanged) was 18.8 per cent compared to a mortality of 10.7 per cent in the exchanged cases who were not treated with Rh

TABLE 4
RELATIONSHIP OF ANTIBODY TITER TO MORTALITY

	Average peak saline antibody titer	*Average peak blocking antibody titer*
Fatal cases, 26	257.6	1 to 64
Living cases, 84	110.0	1 to 32

TABLE 5
COMPARISON OF EFFECTS OF PREMATURE INDUCTION AND SPONTANEOUS DELIVERY

Treatment	*Number of cases*	*Living*	*Neonatal death*	*Mortality*
Spontaneous	89	73	16	18%
Cesarean section	18	8	10	55.5%
Total	107	81	26	

TABLE 6
RESULTS OF TREATMENT WITH Rh HAPTEN

	Total cases	*Kernicterus*	*Mortality rate*
Cases treated with Rh hapten	32	5 (15.6%)	6 (18.8%)
Control cases	65	12 (18.4%)	7 (10.7%)

hapten. Serologists generally believe that this method of treatment has been completely discredited.

Although most attempts to treat the sensitized mother with ACTH and cortisone have thus far failed, the possibilities of hormone therapy have perhaps not been adequately evaluated.[25]

As previously stated, most babies born with active or incipient erythroblastosis showed no symptoms or signs of the hemolytic process at birth. An oxalated or heparinized sample of cord blood was the most valuable specimen for diagnosis and evaluation of the criteria for treatment. A positive direct antiglobulin Coombs' test established the diagnosis definitely, and, although a negative test usually excludes the diagnosis, a "false" negative can occur and a negative test was not relied upon entirely if other factors, such as bad maternal history, were elicited and homozygosity had been established in the father.

Additional tests which were performed on the cord blood or on the infant capillary blood if the cord blood was not kept, were as follows: hemoglobin, blood grouping, Rh typing, serum bilirubin, reticulocyte count, normoblast count, white blood count, and differential count. Of these tests, hemoglobin concentration was the single most valuable test. A majority of workers in this field now regard a cord hemoglobin of less than 13.6 gm. as an indication for exchange transfusion if the Coombs' test is positive. A hemoglobin level of less than 14.5 gm., if taken from infant capillary blood, is likewise a well established index. A low serum bilirubin value in cord blood or capillary blood at birth may be misleading, since most of the pigment may have escaped through the placenta. Because any sharp rise in serum bilirubin concentration or a level above 12 mg. per cent of indirect bilirubin is known to be a serious prognostic omen, this finding should be regarded as a real indication for exchange transfusion in erythroblastosis. Indeed, a level of 20-mg. per cent, largely "indirect" after an exchange, is an indication for repeating the replacement. The average peak serum bilirubin in our fatal and kernicterus cases at Northwestern and University hospitals was 25.3-mg. per cent, whereas, in patients who survived, the average total was 11.01 per cent. The average hemoglobin was 10.6 gm. in the fatal cases and 14.8 gm. in the survivors. A high reticulocyte count in the presence of hemolytic disease was found to be valuable in deciding upon the need for exchange, whereas normoblastemia was a relatively unreliable guide. Leaders in the study of hemolytic disease of the newborn now recommend exchange transfusion when most of the usual criteria are lacking, if the maternal history is bad and the father is homozygous. It is contended that prematures born under these circumstances should be exchanged, if the Coombs' test is positive in spite of normal hemoglobin and serum bilirubin levels.

The better over-all results of exchange transfusion as compared to early interval transfusion in the first 107 cases treated at Northwestern Hospital is shown in table 7.

Even though the criteria for performing exchange transfusion were perhaps too conservative in the beginning, the exchange transfusion cases showed better results than those achieved in a series of milder cases in which early interval transfusion was employed. Mollison and Walker[21] carried out a controlled study on 477 infants whose treatment was predetermined by chance. The mortality in the exchange group was 13 per cent as compared to 37 per cent for those treated by early simple transfusion.

TABLE 7
NORTHWESTERN HOSPITAL CASES TREATED BY EXCHANGE TRANSFUSION

Total cases—107		
Total cases	66	
Kernicterus death	7	
Erythroblastosis fetalis nonkernicterus deaths	4	Total deaths—11, 16.6% mortality
Kernicterus living	0	
CASES TREATED BY EARLY MULTIPLE TRANSFUSION		
Total cases	41	
Kernicterus deaths	8	Total deaths—12, 25% mortality
Nonkernicterus deaths	2	
Kernicterus living	2	

TABLE 8
179 CASES OF ERYTHROBLASTOSIS TREATED AT UNIVERSITY OF MINNESOTA AND NORTHWESTERN HOSPITALS BETWEEN 1945 AND 1951

	1945–51	*1951–54*
Total cases	113	66
Kernicterus	17 (15.04%)	4 (6.06%)
Average bilirubin levels in kernicterus cases	25.0-mg. %	25.6-mg. %
Average bilirubin levels in nonkernicterus cases	10.81-mg. %	13.31-mg. %
Number of exchanges	36 (32.1%)	45 (68.1%)

TABLE 9
RESULTS OF THE USE OF EXCHANGE TRANSFUSION IN RICHARDSON HOUSE, BOSTON*

	1-1-45 to 10-31-46	*11-1-46 to 3-31-49*	*4-1-49 to 6-30-51*	*7-1-51 to 6-30-53*
Exchange transfusion	0	36 (63%)	61 (90%)	38 (79%)
Kernicterus	6 (30%)	6 (10.5%)	0	0

*Adapted from Allen, Fred H., Jr., and Diamond, Louis K.: Prevention of kernicterus. J.A.M.A. 155:209, 1954.

Of 4 infants who developed kernicterus after exchange, 3 were prematures. Severely affected mature infants with cord hemoglobins below 11 gm. and severely affected prematures with hemoglobins above 11 gm. were the 2 classes showing the greatest improvement as compared to controls. Severely affected prematures with less than 11 gm. of hemoglobin had a high mortality in spite of exchange. Since no treatment of the sensitized mother will prevent kernicterus, with the possible exception of hormones, and since kernicterus is closely correlated with prematurity, it seems advisable to avoid induction of birth before thirty-eight weeks.

As stated previously, Mollison and Walker[21] favor a low cord hemoglobin as an indication for transfusion. They regard any value below 13.6 gm. in cord blood and 14.5 gm. in capillary blood in the presence of a positive Coombs' test as an indication for exchange. Our data tend to substantiate this inasmuch as 75 per cent of the patients on whom an exchange transfusion was done had cord hemoglobins of 14.0 gm. or less.

Of 179 cases studied from the University and Northwestern hospitals in Minneapolis, 113 occurred before 1952 and 66 cases after that date (table 8). The pronounced reduction in the rate of occurrence of kernicterus from 15.04 per cent to 6.06 per cent seems to correlate well with the increased use of exchange transfusion (32.1 per cent of the cases before 1952 and 68.1 per cent of the cases since 1952). These data agree well with those of Allen and Diamond (table 9) who have reported that in over 200 cases of erythroblastosis, which they have treated since 1948, they have had no instance of clinical kernicterus.[10]

Experience to date indicates that a liberal attitude toward the use of exchange transfusion has appreciably reduced the incidence of kernicterus. Indeed, cases of hemolytic disease of the newborn that are treated promptly and adequately do not suffer from clinical kernicterus as a complication.

In order to remove hemolyzing red cells as well as large quantities of bilirubin and to replace these with cells that are not susceptible to the action of maternal antibodies, exchange transfusion should be done in most cases of active hemolytic disease of the newborn.

By suppressing both hemopoiesis and the accumulation of toxic products of hemolysis, kernicterus may be prevented. Kernicterus is the only important cause of death after the first day of life. It can be prevented by exchange of blood and this procedure may be repeated two or three times, if necessary, to keep the bilirubin from rising above 20 mg. per 100 cc.[26,27]

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Diffuse Brain Damage in Children: Behavioral Manifestations

HUNTER H. COMLY, M.D.
Iowa City, Iowa

The consequences of brain injury in the infant and child range from the very subtle to the extremes wherein gross disturbances are seen in nearly all sectors of functioning. With focal damage resulting in spasticity or paralysis, the diagnosis is usually obvious and the responses to the child's malfunctions on the part of parents and society are rather likely to be appropriate. But with the types of injury under present consideration, the responses to the child's disturbed functions are too often detrimental. This review is offered with the expectation that it will increase the frequency of diagnosis in the child with subtle involvement and hence foster a happier life for him and his associates.

The complaints about the child cover a wide range of aberrancies. "He can't sit still." "His play is aimless." "He's temperamental." Mothers say, "I can't get close to him." From the school we hear that he presents special learning disabilities. He forgets what he has just learned. Arithmetic is probably his hardest subject. He gets stuck on an idea and keeps talking about it. He is awkward and fidgets. He may daydream excessively. Punishment does no good. Teachers say, "He's a nuisance in the classroom — he has no friends — the children don't know how to take him — you can't tell how he will be from one day to the next." Thus the vague outlines of a clinical picture characterized by hyperkinesis, brief attention span, and unpredictable moods are sketched by the informants. The significant historic data; description given by parents of the child; findings at physical examination, at interview, and from psychologic tests; and the electroencephalogram all lend details required to develop a more certain delineation.

During the interview with the parents, we may learn that the mother's pregnancy was complicated by a febrile illness during the early months. She may have been anemic or suffered toxemia or other difficulties. Premature separation of the placenta may have occurred. The child may have been born prematurely or, if one of twins, is probably the second born. The labor may have been too short or unduly long. The patient's neonatal course may have been, by report, quite uneventful. More significantly, one or more features such as lassitude, irritability, cyanotic periods, excessive jaundice, dehydration, vomiting, colic, and so forth may have characterized the first days.

Sometimes, severe infection such as pertussis, pneumonia, or meningitis with great prostration occurred in the early months. Frequently, neuromuscular development follows a normal schedule or the variations from the norm are, taken alone, insignificant. In the postinfancy years, an illness characterized by fever, delirium, convulsions, marked apathy, and coma succeeded by paralyses, ataxias, regressions in habits and motor control, sleep reversals, and personality changes may be of crucial significance. The delayed sequelae of cerebral concussion may result in similar behavior patterns, with little or no clear-cut neurologic evidence of focal damage.

A systematic review of the child's functions, skills, behavior deficiencies, and peculiarities is essential to diagnosis. Questions range in each area from general to specific, as an anxious and suggestible informant may be misleading.

Regarding the patient's motility, the following points may be indicative of brain injury. We ask the parents to describe his posture, carriage, or gait and to imitate, if possible, any tics or stereotyped or recurrent patterns of motion. We inquire about the occurrence of petit mal, grand mal, or psychomotor convulsions. We wonder about myoclonic jerking during sleep, demonstrate what we mean, and ask the parent to estimate the frequency. The assessment of hyperkinesis by history is aided by asking for descriptions of the way the child responded when the parents read to him or showed him pictures in children's books at bedtime. His attention span and responses to children's phonograph records may be suggestive. In our experience, the child with an injured brain doesn't get glued to the television screen, and parents usually learn to avoid taking him to movies. If barbiturates were

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given for restlessness and hyperactivity, often they were stopped, as they increased the problem.

We find that speech development may be delayed or normal. The normal perseveration, however, may be exaggerated, and the usual reversals, such as "mazagine," may persist beyond the usual time. The content of speech offers clues to the child's thinking and its aberrations. He may ask the same question repeatedly and seemingly without reason. Misconceptions and false beliefs may be tenaciously held.

The child with an injured brain may be inordinately callous to physical pain or, conversely, fearful and unduly dependent, needing much solicitude when threatened with or actually suffering from physical pain. The child who is callous to pain is apt to be reckless and daring and sometimes sadistic and remorseless. The latter characteristics, however, seem to be related more to the way the environment has dealt with him than to the intrinsic organic defects. Frustration tolerance is often less than would be expected for his age and is related again to environmental factors as well as the brain defect.

Variability in mood is often pronounced from moment to moment as well as from day to day. Often, parents observe greater fluctuations in this regard than with their other children whom they can understand and explain the disturbances. They can see them as related to situations, but are perplexed by the vagaries of the patient's mood.

Disturbances in emotional expressiveness are difficult to describe, but some clues are often elicited. The change from sunny smiles to tears is often abrupt. Laughter is sometimes silly, too loud or long, or explosive. Instead of a smooth shift of feeling tones, there may be sharp changes lacking the customary blending from one phase to another. Impulsiveness may take many forms – in speech, in action, in making decisions, and so forth. Judgment may be erratic because of unevenly controlled impulsiveness.

Sometimes, clues to the child's difficulty in spatial orientation and visual motor perception and coordination can be elicited during the interview. An 11-year-old girl with an average Stanford-Binet I.Q. persisted in confusing north and west despite much effort to orient her. Other children persist in getting shoes on the wrong feet and clothes on inside out.

The report from school is vital. The teacher can be more objective than the parents and has a broader background from which to draw significant comparisons. She can evaluate the child's attention span and the quality of his thinking. Samples of his writing displaying reversals of letters and perseverative trends may be provided. The teacher may be alert to the child's tendency to momentarily forget newly learned material, as in reading and spelling, and recognize it as quite unusual. She can describe how he treats his peers and their relationship to him.

In the instances when we are dealing with a highly problematic diagnosis, we are often left quite in doubt about the significance of the suggestive data. Each or even several peculiar items taken singly or grouped are not so deviant as to be pathognomonic. Often it is the sheer number of minor variations and peculiarities elicited by a careful history that in composite lends weight to the supposition of subtle brain injury.

The interview with the child is best held in a quiet room with a few toys available. The examiner endeavors to keep his activity minimal in order to encourage spontaneity and limit external stimulation. He watches for the slightly propulsive gait, the suggestion of athetosic movements almost blended with normal gesticulations. He focuses his attention on the relationship as it develops. "Is the child too forward, brash, or bold?" "Is this little girl a bit too affectionate?" In the preschool child, he watches for meaningful themes in the child's play. "Are they sequential or are they so broken by attention drifts as to be confusing and aimless?" Perseverations in a given theme may be as important clues as aimless shifting from toy to toy. With the older child, the examiner encourages conversation by asking general questions requiring elaboration. He selectively attends to speech patterns, listening for dysarthria, propulsions, and inappropriate intonations, rhythms, and blockings. He may notice sudden shifts in thought content and be at a loss to find the linking associations.

The play interview paves the way for cooperation during the physical examination. Having the parent in attendance is often helpful, as maximal cooperation is essential.

Very often there are no clear-cut abnormalities noticed during the neurologic examination. Yet, tendencies are important. Signs may be fleeting and not reproducible at will. We think we notice some exophoria, so we test the oculomotor movements. Eye rotations seem all right. Fixation is normal. Nystagmus is minimal or absent. We are momentarily distracted. We look back at the child and think, "There's that peculiar cast to the eyes again, or did I really notice it?" We look at the optic disks, and they appear normal. Our patience is sorely tried. We think, "Can't this child keep his eyes focused for a few seconds?" We observe his postural and righting reflexes and his sense of balance and then evalu-

ate the smoothness of his associated motor movements. Confronted with a list of equivocal neurologic signs, we sit down to record our observations, meanwhile noticing how the child dresses himself. We observe the sequence he employs – the evidences of confusion or attention drifts. We notice the parent-child interaction during the process.

We discuss the findings on certain standardized psychologic tests with the clinical psychologists. We inquire about motor control, distractibility, impulsiveness, evidence of hyperkinesis, figure-ground reversals, and apparent tolerance and characteristic patterns of reaction to frustration. Perseveration trends and body image distortions are sought. The quality of verbal abstractions is assessed. We are especially interested in the degree of consistency of the child's performance on the various subtest items of the Wechsler Intelligence Scale for Children, the Bender Gestalt test, and the Benton Visual Retention test. Qualitative judgments about performance on these tests and on the Goodenough test are important.

In our experience, when there is a strong suspicion of diffuse brain injury based on the above approach, over 90 per cent of the children will have abnormal electroencephalograms.

DISCUSSION

We have been impressed by the frequency with which we see children referred with a wide variety of behavior disturbances in whom the possibility of nonfocal brain injury has been overlooked. We feel it must be considered in all cases. A positive or strongly presumptive diagnosis frequently prepares the way for rational treatment taking cognizance of the child's special limitations. The incorrigible, overpunished, and scapegoat child becomes a child with concrete problems. Another set of influence technics is gladly applied when reasons for the child's, parents', and teacher's difficulties are found.

We have attempted to adopt a comprehensive point of view regarding the etiology of the primary defects and the behavioral manifestations encountered clinically. It is based on much established fact but necessarily includes considerable speculation. We know the brain can be damaged in utero by the virus of German measles and that embryonic tissues are excellent media for viral propagation. We believe other viruses probably are responsible for our findings in these disorders and that the encephalopathy may be produced before or after birth, resulting at times in undetectable changes which only later find symptomatic expression in behavior. The newborn laboratory animal can survive considerable oxygen deprivation, but we don't know what behavioral aberrances would appear later in humans subjected to the same stress. Rosenfeld and Bradley[1] found that a behavioral syndrome similar to the one outlined here existed 8 times as frequently in children who suffered asphyxia neonatorum or pertussis before 3 years of age as in a control group whose histories did not include asphyxia or pertussis under 3 years of age. It seems likely to us that the relative fetal anoxia which may attend prolonged labor or accompany premature partial placental separation, oversedation, and so forth, may result in a viable but subtly damaged baby.

Speculation would lead us to anticipate finding widespread but subtle tissue changes similar in distribution but less extensive than those found after carbon-monoxide poisoning or encephalitis. Decreasing mortality statistics in the newborn period, especially with premature babies, will probably result in the relatively increased frequency of these syndromes. Similarly, antibiotic therapy for the meningitides and encephalitides, though resulting in laudable mortality reductions, will inevitably result in a relative increase of slightly damaged children.

Since October 1952, we have been testing children's postural and righting responses as suggested by Silver.[2] In children over 6, a simple clinical test often strongly confirms our suspicions of diffuse brain damage. With the patient standing and his eyes closed, the arms are extended parallel to each other. The head is then passively rotated as far as possible without discomfort. Before 5 or 6 years of age, there may be wide divergence of the arms, marked choreiform movements, and rotation of the body on its longitudinal axis. After 6, the posture becomes more static, divergence of the arms is minimal, and the body does not rotate with the head. Abnormal responses consist of exaggerations of the tonic-neck and neck-righting responses or, conversely, marked rigidity with convergence of the outstretched arms.

In dealing with children who act out their disturbances in destructive ways, the utmost in clinical judgment is always required in order to estimate accurately the relative significance of organically determined disinhibition versus the pressures from the parents who unconsciously foster and vicariously enjoy the havoc created by delinquent children. Johnson and Szurek[3] have presented the dynamics of these tragic situations in an admirable fashion, clearly describing how the neurotic parent may unconsciously corrupt the child's conscience and make

it impossible for him to develop appropriate inhibitions. With these concepts in mind, we observe the parental attitudes carefully, constantly on the lookout for the inappropriate and sanctioning smile as they describe the child's destructiveness. The healthy parent readily conveys his serious concern, and his face expresses the grave and forbidding way he feels about the child's naughtiness. There is an element of hazard in telling neurotic parents their child has brain disease. This makes it easy for them to go on fostering the difficulties, secure in the belief that all the abnormality resides in the child. But, fortunately, in our experience the parents of the child with a damaged brain who is referred because of disorderly behavior are often the healthiest, best balanced parents we see. This fact alone may make the diagnosis more certain.

Treatment may be extremely rewarding. Environmental manipulation, counselling with the parents, and medication are all powerful tools. The hyperkinetic, impulsive, distractible child, labeled and reacted to as incorrigible, may respond dramatically to a new teacher and classroom. The teacher must know the diagnosis, screen the child from distractions, and provide special educational devices, such as books with large print. This aspect of therapy is thoroughly discussed in a book by Strauss and Lehtinen[4] on the brain injured child. Painless removal from the group before the child's behavior becomes chaotic and contagious is essential. Special educational consultants can help the teacher build an individualized program. Parents can be helped to understand the special limitations of the child and, freed of feelings of guilt and personal failure, can become more objective and constructive in their interactions with him.

Bradley[5] has demonstrated the effectiveness of Benzedrine and Dexedrine in behavior disorders. The amphetamines tend to subdue the hyperkinetic child, increase his attention span, and stabilize his mood. Dosages in Bradley's study ranged from 10 to 40 mg. a day for Benzedrine and from 5 to 30 mg. for Dexedrine. In our experience, these are the children who are apt to benefit markedly from these drugs. A brief case history will illustrate this:

CASE REPORT

Jimmy R., 9½ years old, was referred because of school failure. He was the eldest of 2 boys. His parents were very competent and well adjusted. He was delivered with instruments after an uneventful pregnancy and a forty-hour labor. As a toddler and runabout, he was overactive and callous to pain. His mood was unpredictable and his attention span relatively short. In school, he seemed confused and his work was inconsistent. Arithmetic, language, and writing were hardest for him. He left out whole sections of his assignments and seemed genuinely surprised when his oversights were pointed out to him. Psychologic tests revealed a verbal I.Q. of 120, performance I.Q. of 106, and a full-scale I.Q. of 115. There was, however, marked variability in performances among subtests. The Bender Gestalt drawings were compatible with the diagnosis of brain injury. Reversals, perseverations, and difficulties in visual perceptual coordination characterized the record. The interviewer noticed tics, grimaces, and stereotyped expressive movements. Neurologic examination was normal except for abnormal postural and neck-righting responses. His affect was shallow. A diagnosis of chronic brain syndrome probably due to fetal cerebral anoxia was made. Dexedrine Sulfate was prescribed in increasing amounts, and reports from the school were obtained weekly. No change was noticed when 5 mg. was administered morning and noon. When 7.5 mg. was given twice daily, it was noticed that he copied all of his arithmetic examples correctly. After five days, while receiving 10 mg. twice daily, his performances in language and spelling were reported as improved. While receiving 15 mg. morning and noon, he had trouble falling asleep, and the noon dose was reduced to 10 mg. After two weeks at the 25-mg. level, the teacher reported a considerable improvement in his arithmetic. The mother reported, "He is more contented and relaxed. He now spends an hour happily pasting stamps in his stamp book. This never occurred before."

In the past year we have seen 20 such children whose responses to high doses of Dexedrine have been quite favorable. We feel that, since the amphetamines are safe drugs, it is worth while to give them a therapeutic trial in doubtful cases, increasing doses gradually from 5 to 40 mg. a day in 2 daily doses. We usually plan to postpone informing the teacher about the use of medication in the hope that an evaluation unaffected by suggestion or wishful thinking can be obtained. The diagnostic problem may be further clarified, in some instances, by this device.

SUMMARY

Some clinical features of children with behavior disorders associated with subtle and probably widespread brain damage are presented. Data from interviews with parents and child, physical examination, psychologic tests, and electroencephalograms may form a composite picture rendering the diagnosis quite certain. Treatment depends on diagnosis and is briefly outlined. The usefulness of Benzedrine and Dexedrine is emphasized.

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Pathologic Lesions Associated with Respiratory Disturbances in the Newborn

JAMES B. AREY, M.D.
Philadelphia, Pennsylvania

Approximately 5 per cent of all deaths occur during the first month of extrauterine existence, and most of the severe illnesses during this period are manifest as respiratory disorders. Such disorders are usually the result of pulmonary or intracranial lesions, which may be difficult or impossible to differentiate clinically. In general, however, respiratory disturbances of peripheral (pulmonary) origin are associated with dyspnea and vigorous respiratory movements, whereas those of central origin are characterized by apnea or by infrequent, weak, irregular respiratory movements.

Not only are pulmonary and intracranial lesions important as an immediate cause of death in newborn infants, but similar lesions of less severity are often present as contributory factors rather than as primary causes of death. Thus, in a series of 102 liveborn infants who died during the neonatal period, significant pulmonary lesions indicative of the primary cause of death were present in 40, more than one-third, of the infants. Similar lesions were present in an approximately equal number of infants but were considered contributory rather than primary causes of death. In this same group of infants, cerebral lesions were responsible for 30 deaths; in less than one-sixth of the infants less severe cerebral lesions were present as possible contributory lethal factors.[1] This latter type is of particular importance, since, if death does not occur from other causes, these lesions may become manifest in later infancy or childhood as serious neurologic disorders.

Prematurity, although an extremely important factor in the production of respiratory disturbances in the neonatal period, should be accepted as a primary cause of death only in very small previable premature infants. Complete postmortem examinations will usually reveal some factor in addition to prematurity which is responsible for death in the newborn period. Similarly, atelectasis should not be accepted as a primary cause of respiratory disturbances or of death in the neonatal period. Small areas of atelectasis are probably normal for several days after delivery,[2] and the cause of persistent or severe atelectasis is usually demonstrable at postmortem examination by macroscopic study of the contents of the cranial cavity or by histologic examination of the lungs.

PULMONARY HYALINE MEMBRANES

Pulmonary hyaline membranes are now the most frequent significant pathologic finding in premature infants dying during the neonatal period. Infants with pulmonary hyaline membranes may manifest symptoms at the time of delivery, but, in approximately one-half of the infants, the onset of symptoms is delayed until a few hours after birth. In either event, the infant with pulmonary hyaline membranes exhibits severe dyspnea, cyanosis, grunting respirations, and suprasternal and infracostal retractions within a few hours after delivery. In spite of vigorous respiratory movements, auscultation of the chest while the infant is not crying usually reveals little or no apparent exchange of air.

Clinically, the occurrence of such symptoms at or shortly after birth is rather strong presumptive evidence of the presence of pulmonary hyaline membranes. However, an unequivocal diagnosis can be established only by histologic examination of the lungs at the time of autopsy. Although the clinical diagnoses must thus be only presumptive, there is evidence to indicate that a number of infants with pulmonary hyaline membranes may recover and that the presence of such membranes is by no means uniformly fatal.

At postmortem examination, lungs containing hyaline membranes are characteristically deep purplish red and noncrepitant and incompletely fill the pleural cavities. Since other pulmonary lesions may simulate pulmonary hyaline membranes macroscopically, positive diagnoses are dependent upon histologic examination. Histologic studies reveal apparent widening of the interalveolar septa as a result of atelectasis, with approximation of adjoining interalveolar septa. There is intense congestion, and, in sections stained with hematoxylin and eosin, bright pink,

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homogeneous to granular membranes line a number of the respiratory bronchioles, alveolar ducts, and alveoli. Scattered air spaces may be hyperexpanded, and the subsequent occurrence of interstitial emphysema, pneumomediastinum, and spontaneous pneumothorax are relatively infrequent but important complications in the infant with pulmonary hyaline membranes who survives longer than twenty-four to forty-eight hours. An inflammatory cellular exudate is usually absent in lungs with pulmonary hyaline membranes in infants dying within twenty-four hours after delivery, but bronchopneumonia is commonly present in association with such membranes in infants surviving for longer periods of time.

With respect to the pathogenesis of these membranes, there is certainly no unanimity of opinion. That premature delivery and delivery by cesarean section predispose to their occurrence is generally accepted, but the manner in which these factors favor the development of membranes is not clear. Furthermore, hyaline membranes do not occur unless extrauterine respiratory movements have persisted over a period of at least one hour.[3] Beyond these 3 facts, any discussion of the pathogenesis of pulmonary hyaline membranes is almost entirely theoretical. Although probably the majority of investigators believe that the membranes are formed from protein derived from the amniotic fluid, such an origin is certainly not accepted by all. There is evidence to support the view that these membranes are formed from protein derived from the blood of the fetus or infant. Thus, attempts to produce pulmonary hyaline membranes by intratracheal injection of amniotic fluid alone into living animals have been uniformly unsuccessful, and hyaline membranes have been produced experimentally by a variety of means not employing amniotic fluid. Furthermore, similar membranes may be found in older children and adults, in whom aspiration of amniotic fluid is obviously impossible. The membranes may occur in association with rheumatic pneumonitis, radiation pneumonitis, influenzal pneumonia, uremia, and a variety of other conditions. In many, if not all of those conditions in which pulmonary hyaline membranes are observed in later life, there appears to be some degree of vascular damage. Furthermore, increased capillary fragility is one of the inherent defects of the premature infant, and pulmonary hyaline membranes are observed far more frequently in premature infants than in those born at term. Therefore, it would seem possible that vascular damage might be the common denominator in the development of these membranes both in newborn infants and in older children and adults. Such vascular damage, perhaps enhanced by anoxia in the premature infant, would allow the escape of protein and fluid from the blood into the alveolar spaces. With subsequent resorption of fluid, concentration of protein, and inhalation of air, the concentrated protein might be compressed against the alveolar walls to form the characteristic pulmonary hyaline membranes.

A corollary to the above theory has recently been suggested and certainly warrants further study. The period of birth is one of tremendous vascular readjustments with closure of the foramen ovale and ductus arteriosus and increased pulmonary blood flow. If, through abnormalities in this normal vascular readjustment, pulmonary blood flow were to be abnormally increased, as by failure of the ductus arteriosus to close, the resultant pulmonary congestion might have an effect similar to that described above, with escape of protein and fluid into the alveolar spaces and subsequent formation of pulmonary hyaline membranes.

Experimentally, pulmonary hyaline membranes have been produced by a variety of methods, including intratracheal injection of egg albumin, oxygen poisoning, carbon-dioxide poisoning, and bilateral vagotomy.[4] Intratracheal injection of amniotic fluid alone into living animals has failed to produce these membranes, but the injection of larger amounts of this fluid into the excised lungs of experimental animals has resulted in the formation of such membranes.[3] More recently, Laufe and Stevenson have produced pulmonary hyaline membranes in vivo by the intratracheal injection of mixtures of amniotic fluid and plasma.[5] Membranes produced by this means have been associated with atelectasis and pulmonary congestion comparable to that seen in the newborn infant, whereas the other experimentally-produced hyaline membranes have not been associated with these findings. Ahvenainen was able to produce hyaline membranes in the lungs of kittens by intratracheal injection of a mixture of amniotic fluid, hydrochloric acid, and pepsin. Although some of the kittens developed membranes resembling those in the lungs of newborn infants, all membranes were associated with an inflammatory exudate.[6]

Even in respect to the prevention and treatment of pulmonary hyaline membranes, not all investigators are in agreement. Since cesarean section does predispose to their occurrence, needless sections should be avoided. Although the membranes may be produced experimentally by prolonged administration of high concentra-

tions of oxygen, infants with such membranes are obviously suffering from lack of oxygen, and improvement may be noted following oxygen administration. Therefore, oxygen should be administered to the infant with suspected pulmonary hyaline membranes. The oxygen should be adequately humidified and usually should not exceed 40 to 50 per cent. Whether an actual mist serves either a prophylactic or therapeutic purpose remains to be proved. The use of wetting agents such as Triton WR-1339 or Alevaire does not appear to influence the mortality associated with pulmonary hyaline membranes.[7] Since bronchopneumonia is an important complication in infants surviving more than twenty-four hours, broad-spectrum antibiotics should be given on a prophylactic basis. Such complications as pneumothorax should be recognized early and treated promptly.

Knowledge concerning the nature, cause, prevention, and treatment of pulmonary hyaline membranes is sadly deficient. It is essential that more be learned concerning these membranes, since their frequency is such that further significant reductions in neonatal mortality will occur only after methods of successfully preventing and treating such membranes have been established.

FETAL ANOXIA

Fetal anoxia is responsible for approximately 10 per cent of neonatal deaths and is an important cause of respiratory disturbances in the immediate neonatal period. It is usually the result of some complication of pregnancy or labor, for example, prolapse of the umbilical cord, abruptio placentae, placenta previa, excessive narcosis, and so forth. As such, fetal anoxia may be prevented in some but not all instances.

Clinically, the manifestations of fetal anoxia are usually apparent at or very shortly after delivery. In contrast to pulmonary hyaline membranes, the respiratory disturbance associated with fetal anoxia is characterized by weak, irregular, ineffective respiratory movements, apnea, cyanosis, and, at times, atonia and shock. Such symptoms are similar to those associated with respiratory disturbances of central origin, and it seems probable that they are produced primarily as a result of cerebral anoxia rather than pulmonary changes. Fetal anoxia is thus important not only as a cause of respiratory disturbances and death in the neonatal period but, in some instances, as a cause of permanent cerebral damage in those infants with severe anoxia who recover.

Postmortem examination of infants dying with fetal anoxia usually reveals atelectasis, visceral congestion, and scattered petechiae; the last are noted especially in the thymus and on the serous surfaces. However, these findings are so nonspecific that they do not warrant a diagnosis of fetal anoxia. The diagnosis can be established only by histologic examination of the lungs, with the demonstration of large amounts of amniotic debris in the pulmonary air spaces. It should be emphasized, however, that lethal fetal anoxia may occur in the absence of such pulmonary changes and that the presence of small amounts of amniotic debris in the lungs is a relatively constant finding in infants dying of a variety of causes during the neonatal period. Only the presence of large amounts of amniotic debris within the lungs should be considered as indicative of fetal anoxia. In spite of these pathologic findings, the deaths of most of these infants are probably the result of cerebral damage. Cerebral congestion and petechiae are commonly present, but, because of the rapidity with which death usually occurs, more specific signs of cerebral anoxia are usually lacking.

Although some degree of bronchial obstruction and atelectasis may result from aspirated amniotic fluid and debris, it seems unlikely that this is often important clinically or that it can be relieved by tracheal aspiration. Nevertheless, maintenance of a clear airway by *gentle* manipulative procedures is indicated in infants with signs and symptoms suggesting fetal anoxia. Properly humidified oxygen should be administered as necessary; some physicians advocate the use of oxygen in mist. Bronchopneumonia is an important complication of fetal anoxia, and the prophylactic administration of adequate antimicrobial agents is therefore indicated in all such infants.

INTRAVENTRICULAR HEMORRHAGE

Among the various cerebral lesions responsible for death in the neonatal period, intraventricular hemorrhage is the most common and accounts for approximately 10 per cent of all deaths occurring in the neonatal period, especially in the small, previable premature infant. Signs and symptoms referable to an intraventricular hemorrhage may be present at the time of birth or may be delayed for a period of several hours or even several days after delivery. During this latent period, the infant may manifest no unusual signs or symptoms, and death occurs on the second or third day after symptoms have been apparent for only a few hours. In some instances, however, the infant may appear unusually alert and hyperactive during this latent period. Such signs

in a small premature infant should lead one to suspect the possible subsequent occurrence of an intraventricular hemorrhage. In other instances, however, signs and symptoms directly related to an intraventricular hemorrhage may already be apparent at the time of birth, and death usually follows the appearance of such symptoms within a relatively short period of time.

The clinical manifestations of an intraventricular hemorrhage are predominantly respiratory in nature and are characterized by a very irregular respiratory pattern, apnea, and cyanosis. In addition, irritability, loss of the Moro reflex and, in a few instances, a bulging fontanelle may be noted.

The presence of an intraventricular hemorrhage can usually be predicted at the time of postmortem examination by the appearance of the base of the brain, even before the contents of the ventricular cavities are examined. Abundant blood is present in the cisterna magna and extends anteriorly along the surface of the pons into the interpeduncular cistern or even into the sylvian fissures. The extent of the intraventricular hemorrhage, as well as its source, can be ascertained better if the brain is fixed in 10 per cent formalin for several days before sectioning, thus allowing the blood in the ventricles to harden.

The source of the intraventricular hemorrhage is not always apparent. In some instances, bleeding appears to arise from the engorged vessels of the choroid plexuses. Frequently, however, it results from rupture of a subependymal hemorrhage, which characteristically is located in the region of the terminal vein between the caudate nucleus and the thalamus. It is the occurrence of such subependymal hemorrhages with subsequent rupture into the ventricles that explains the latent period noted clinically. During this period, blood is accumulating in the relatively "silent" subependymal area; only with rupture of this hemorrhage into the ventricular cavity do symptoms become apparent.

Histologic examination of the subependymal hemorrhages about the terminal vein in small premature infants reveals them to be located in a zone of small, dark-staining undifferentiated cells. These "neuroectodermal elements" or "medulloblasts" presumably aid in the subsequent formation of the thalamus and basal ganglia. It seems possible that nonlethal hemorrhages occurring in this zone which do not subsequently rupture into the ventricles might destroy numerous undifferentiated cells and thus lead to subsequent impairment in the formation of the thalamus and basal ganglia, with resultant neurologic sequelae in later life. That damage to this zone with resultant alterations in the basal ganglia may occur in rodents exposed to irradiation in utero has been demonstrated experimentally,[8] but proof that hemorrhage in this region in the newborn may lead to permanent neurologic damage is not yet available.

A variety of theories has been advanced to explain the occurrence of intraventricular hemorrhages in the newborn period, none of which is entirely satisfactory. Suffice it to say that the single most important predisposing factor in their origin is the prematurity of the infant, and that the lesions do not appear to be traumatic in the usual sense, that is, they should not be considered to be the result of poor obstetric management.

The treatment of a newborn infant with an intraventricular hemorrhage is usually quite unsatisfactory. Undue manipulation of the infant should be assiduously avoided. The head may be somewhat elevated, properly humidified oxygen should be administered, and spinal puncture, if performed for diagnostic purposes, may be repeated if an apparent improvement in signs or symptoms results. In general, however, death usually occurs within a few hours after symptoms become apparent.

INTRACRANIAL TRAUMA

Intracranial trauma sustained during delivery is now less frequent than in the past but is still an important cause of serious illness and death during the neonatal period. Although more frequent after a difficult delivery, especially by breech, severe intracranial trauma may occur following an apparently simple, uncomplicated delivery and may even occur during delivery by cesarean section.

Symptoms referable to intracranial trauma are usually apparent at or shortly after birth but (as with intraventricular hemorrhage) may be delayed for a period of two to three days. The manifestations are predominantly respiratory in nature, with apnea, increased irregularity of the respiratory pattern, and cyanosis. A bulging fontanelle may be noted, and varying degrees of somnolence, shock, twitchings, or frank convulsions may occur.

At postmortem examination, intracranial trauma is manifested by tears of the dural septa, usually the tentorium cerebelli, and associated subdural hemorrhage. The tentorial tears, although indicative of increased intracranial stress, are not of themselves lethal, and death usually does not occur in the absence of subdural hem-

orrhage. The subdural hemorrhages noted in the early neonatal period are not encapsulated and are spread diffusely over one or both cerebral hemispheres or in the subtentorial space. At times, subdural taps performed through the coronal sutures may fail to reveal the hemorrhages. In such instances, if clinical manifestations are sufficiently indicative of the presence of such hemorrhages, the subdural taps should be repeated through the lambdoidal sutures. In the absence of dural tears, small amounts of subdural hemorrhage may be anoxic rather than traumatic in origin, but extensive hemorrhages are usually the result of intracranial trauma.

The treatment of infants with intracranial trauma is essentially similar to that described under intraventricular hemorrhage. The infant should not be unduly disturbed, adequately humidified oxygen should be given as indicated, and the head should be slightly elevated. Subdural taps performed for diagnostic purposes should be repeated if blood or fluid is encountered. Vitamin K should be administered, but its value in the presence of traumatic hemorrhages is questionable. Since intracranial trauma is frequently associated with fetal anoxia, prophylactic antimicrobial therapy should be given to lessen the chances of pulmonary infection.

BRONCHOPNEUMONIA

The incidence of bronchopneumonia as a cause of neonatal morbidity and mortality is not known. Although recently reported as being responsible for 10 per cent of neonatal deaths,[1] it seems possible that the incidence is somewhat less at the present time. Nevertheless, bronchopneumonia is important not only as a primary cause of death during the neonatal period but also as a contributory cause associated with such other lesions as fetal anoxia or pulmonary hyaline membranes.

Bronchopneumonia may be present in the early hours of neonatal life or in the stillborn fetus. The symptoms may not be primarily respiratory in nature, and the clinical diagnosis is often not established. The only apparent manifestations may be those of listlessness and refusal to nurse. If diagnosis and treatment are delayed until signs and symptoms are apparent, death will frequently occur before therapy can be effective. Thus, the diagnosis of bronchopneumonia in the neonatal period must be a presumptive one, based upon a high index of suspicion and not upon any characteristic clinical pattern. It has been demonstrated that the incidence of pneumonia in newborn infants increases following premature rupture of the fetal membranes or a prolonged or difficult labor or in association with fetal anoxia. Accordingly, any such history should lead one to suspect the subsequent occurrence of pneumonia and should be an adequate indication for the prophylactic administration of suitable antimicrobial agents. Since the symptoms may be nonspecific or obscured by other causes of respiratory difficulty, such as fetal anoxia or pulmonary hyaline membranes, such prophylactic measures are essential in an attempt to prevent needless deaths from infection during the neonatal period.

Since gram-negative bacilli are frequent pathogens during the neonatal period, the use of penicillin alone is often inadequate for the prevention or treatment of pneumonia. Instead, penicillin should be administered in conjunction with a broad-spectrum antibiotic; if streptomycin is used, it should be discontinued after three days and a broad-spectrum antibiotic substituted if further therapy seems indicated.

At postmortem examination, the diagnosis of pneumonia in infants dying during the neonatal period is usually dependent upon histologic examination of the lungs; macroscopic evidence of consolidation or pleural exudate is usually absent. Histologic sections should be prepared from all lobes of the lungs, since the process is often not spread uniformly through both lungs.

CEREBRAL GLIAL SWELLING

A few newborn infants may die suddenly on the second or third day after birth either with no previously recognized clinical manifestations of illness or with signs and symptoms suggesting severe intracranial damage. At postmortem examination, no macroscopic findings indicative of the cause of death may be apparent. Histologic examination of the central nervous system of such infants may reveal numerous swollen glial cells with abundant cytoplasm and eccentrically placed nuclei in the white matter of the cerebral cortex, the internal capsule, the corpus callosum, and sometimes in the white matter of the cerebellum.

The significance, if any, of such glial swelling is not apparent at the present time, and increased awareness of its existence has led to the demonstration of minor degrees of this change in many infants dying of a variety of causes. It is possible that no characteristic clinical pattern is associated with such glial swelling and that it is of no significance. Nevertheless, recognition of its occurrence and even of its questionable significance may lead to more frequent histologic studies of the central nervous system of infants dying during the neonatal period, and it thus

seems worthy of brief mention. Only further studies will prove or disprove the importance of these observations.

CONCLUSIONS

Complete postmortem examinations will reveal pathologic lesions associated with most of the severe respiratory disturbances encountered in infants dying during the neonatal period. A causal relationship between the morphologic and functional alterations can be established in many instances, but sometimes it may be impossible to determine whether the morphologic changes are the cause or the result of the disturbed respiratory pattern.

Since the responses of the newborn infant to a variety of stimuli — anoxic, infectious, or traumatic — are relatively limited, the clinical manifestations of various pathologic processes in the newborn period are often indistinguishable. As a result, clinical diagnoses of infants ill during the neonatal period are especially inaccurate, and determination of the cause of death during this period is properly made only by complete postmortem examination. However, the pathologic findings can be interpreted intelligently only when they are correlated with careful clinical observations. Thus, the pediatrician and pathologist are dependent upon each other for a better understanding of the causes and nature of respiratory disturbances encountered during the newborn period. Recognition of this interdependence should aid in the reduction of neonatal mortality.

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Vitamin A blood levels of children with rheumatic fever are diminished in the acute and early subacute stages of the disease and during intercurrent respiratory infections. The deficiency also occurs with severe cardiac damage and passive congestion of the liver, during acute exacerbations of the rheumatic process, or when the intake of vitamin A and carotene has been inadequate for some time, report Pauline Wang, M.D., and associates of the State University of Iowa, Iowa City. The diet of these patients should be supplemented with 3,000 to 5,000 I.U. of vitamin A.

Pauline Wang and associates: Am. J. Dis. Child. 87:659-672, 1954.

Control of Group A Streptococcal Infections and Their Sequelae

LEWIS W. WANNAMAKER, M.D.
Minneapolis, Minnesota

A SENSE of security now prevails among the medical profession in regard to many of the acute bacterial infections, particularly those initiated by infectious agents which are regularly sensitive to a number of antibiotics. The group A streptococcus is such an organism. It presents no great problems of resistance. The antibiotics have proved to be powerful tools for the control of group A streptococcal infections, acute rheumatic fever, and acute glomerulonephritis. Yet the adoption at this time of a complacent attitude toward these diseases is indefensible, for many problems of both academic interest and practical concern remain. The purpose of this paper is to review some of the progress which has been made in the understanding and control of these related diseases and to point out some important deficiencies which still exist.

THE ROLE OF INFECTION

It seems hardly accidental that, to date, all successful attempts to control acute rheumatic fever and acute glomerulonephritis have been directed toward the control of the preceding streptococcal infection. The success of these approaches is a reflection of the dependability of streptococcal infection as a harbinger of these more serious complications. Indeed, there is abundant clinical, bacteriologic, serologic, and epidemiologic evidence that acute rheumatic fever and acute glomerulonephritis are quite regularly preceded by a streptococcal infection. In addition, a more limited amount of supporting data is now available from studies on experimental animals. A comprehensive historic review of the accumulated evidence from these various sources is beyond the scope of this paper. Instead, the data will be presented briefly with some attempt to explain the apparent discrepancies and to point out certain implications concerning pathogenesis and control.

Clinical recognition of the association of infection, particularly tonsillitis, with the development of rheumatic fever began to emerge as early as the eighteenth century, and a number of reports mentioning the frequent association appeared during the following century.[1–4] The occurrence of carditis and arthritis following scarlet fever has been a clinical observation for many years, but not until relatively recently was it fully appreciated that these special features of scarlet fever are indistinguishable from acute rheumatic fever.[5,6] Acute hemorrhagic nephritis has long been known as a late complication of scarlet fever,[7] and attention has also been drawn to the occurrence of acute nephritis after streptococcal infections of the skin.[8,9]. The fact that some patients with clear-cut acute rheumatic fever or acute glomerulonephritis deny any preceding infection whatsoever or recall an illness which sounds more viral than bacterial in nature has been and still is a matter of concern to some clinicians. However, the occurrence of inapparent and atypical streptococcal infections[10] is a reasonable explanation for these discrepancies, and such patients usually show laboratory evidence of a recent streptococcal illness. Because these types of infection ordinarily escape clinical detection, they are serious deterrents to the over-all effectiveness of control programs which depend on the recognition and treatment of streptococcal infections.

The hemolytic streptococcus was singled out as the infective agent in the pathogenesis of acute rheumatic fever almost simultaneously by workers on both sides of the Atlantic. The work of Coburn[11] in America and of Schlesinger,[12] Sheldon,[13] and Collis[14] in England drew attention to this organism in the early 1930's. At about the same time, laboratory studies revealed that most strains of hemolytic streptococci causing infection in human beings have a common, serologically identifiable polysaccharide. Such strains have been designated by Lancefield[15] as belonging to group A. In this group, about 40 types have been identified serologically on the basis of a protein component, designated as M protein. With few exceptions, bacteriologic studies done during the respiratory infection preceding the onset of acute rheumatic fever and acute glomerulonephritis have revealed the presence of group A streptococci.[16–19]. During the latent pe-

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

riod and during the course of acute rheumatic fever or acute glomerulonephritis, group A streptococci are often more difficult to isolate as the number of colonies may be few and they may be overgrown by other flora. Because of this difficulty and because of reliance on the results of a single culture, a false impression has probably been created in the literature concerning the regularity with which group A streptococci persist in the throat. Careful bacteriologic studies, with repeated cultures, have shown that almost all patients with untreated group A streptococcal infections, whether they develop late complications or not, continue to harbor the infecting organism in the throat for many months and in some instances years.[20] Treatment with antibiotics at any stage may hinder recovery of the organism, although, in individuals who have received antibiotic therapy for only several days, a thorough search frequently reveals that the infecting strain has survived.[21]

Some attention should be given to the persistence of streptococci in the pharynx as it has some bearing on practical preventive measures and may, in addition, be a neglected clue in the pathogenesis of acute rheumatic fever. The fact that carriers of group A streptococci are potential risks to susceptible individuals, especially family contacts, has been recognized for some time, although this risk seems to diminish as the carrier state continues.[22] Only recently, however, has it been recognized that the persistence of streptococci beyond the stage of symptomatic infection may represent a hazard to the individual harboring these organisms. This risk is not so much from suppurative complications, which are due in most instances to the acquisition of a new type.[23] Rather, the risk concerns the development of nonsuppurative complications, since, in treating streptococcal infections, eradication of the infecting organism seems necessary in order to prevent rheumatic fever.[20] The significance of the persistence or nonpersistence of the infecting organism has been elucidated in a recent report from the Streptococcal Disease Laboratory.[24] This report indicates that delayed treatment of streptococcal infections—treatment initiated after all signs and symptoms of the respiratory illness have subsided—reduces the incidence of subsequent rheumatic fever. Such treatment eradicates the infecting organism but does not appreciably inhibit the antistreptolysin 0 response. This finding does not preclude the importance of other antibodies in the pathogenesis of rheumatic fever, particularly type-specific M antibodies which appear late and may, therefore, be inhibited by delayed treatment, but it does tend to direct reasoning concerning pathogenesis away from antibody and toward the effect of persistent streptococci or streptococcal products. It has also aroused renewed interest[25] in the reports of Green[26] and of Collis[27] that hemolytic streptococci can sometimes be cultured from the heart valves of patients dying with acute rheumatic fever. There has been no further confirmation of these reports, and none might be anticipated in an age when few patients come to postmortem without a generous trial on antibiotics. Recently, Denny and Thomas[28] have shown that group A streptococci can persist in the tissues of rabbits for long periods of time and that bacteremia can sometimes be provoked in rabbits with latent infections by the administration of cortisone. However, attempts to demonstrate bacteremia in patients with acute streptococcal infections and in patients with active rheumatic fever who were receiving cortisone have been unsuccessful. It is possible, of course, that streptococci may persist in the tissues in some filtrable and not easily cultured form. Although L-forms have been reported in connection with some strains of streptococci,[29] their importance in the pathogenesis of these diseases is at the moment purely conjectural.

Aside from the theoretic implications of the delayed-treatment study, it is of practical value in the control of these diseases, since it demonstrates that rheumatic fever can often be prevented even if specific treatment is begun quite late in the course of a streptococcal infection.

Following the development of technics for the demonstration of antibodies to the intracellular[30,31] and extracellular[32–35] components of group A streptococci, it has been shown that serologic evidence of a recent streptococcal infection can be obtained in most patients with acute rheumatic fever or acute glomerulonephritis. The most satisfactory evidence is available in patients from whom serum specimens are obtained at the onset of the streptococcal infection and again three or four weeks later. In such cases, the change in titer can be determined. In most clinical situations, however, only a single serum specimen taken at the time of onset of acute rheumatic fever or acute glomerulonephritis is available. The titers taken on single sera are difficult to interpret because of the rather wide variation in the normal population, reflecting varying streptococcal experience and host response at varying previous intervals. Therefore, the evidence for a streptococcal infection in such cases is much more circumstantial. Nevertheless, titers in patients with acute rheumatic fever or acute

glomerulonephritis are on the average much higher than comparable normal control groups and tend to be as high or higher than those in patients convalescent from streptococcal infection who do not develop complications.[36]

Among known streptococcal antibodies, antistreptolysin 0 has been studied most thoroughly and has been used most widely as an indication of streptococcal infection. Approximately 70 to 80 per cent of patients with untreated streptococcal infections develop significant increases in antistreptolysin 0 titer.[37] Among patients with acute rheumatic fever, 85 per cent in one series showed a significant increase in antistreptolysin 0, and 90 per cent showed a titer of 250 units or more at the time of hospitalization for rheumatic fever.[21] Patients with acute rheumatic fever who fail to show an antistreptolysin 0 response often show a rise in titer to one of the other streptococcal antigens, such as streptokinase, hyaluronidase, or desoxyribonuclease. Thus, if a number of antibody tests are performed, serologic evidence of a streptococcal infection can be obtained in almost all patients with acute rheumatic fever.[36]

The intense interest in antibody response which has been manifest among workers in this field in recent years has been prompted by the rather attractive hypothesis that an antigen-antibody mechanism may be involved in the pathogenesis of acute rheumatic fever and acute glomerulonephritis. To be sure, the demonstration that penicillin treatment of streptococcal infections both inhibits antibody formation and prevents rheumatic fever suggests that antibody formation may have something to do with the development of this late complication. Moreover, on the average, patients with acute rheumatic fever produce antibodies in larger amounts than patients with uncomplicated streptococcal infections,[36] and the attack rate for rheumatic fever after observed streptococcal infections can be correlated with the magnitude of the antistreptolysin 0 response.[38,39] This suggests that rheumatic subjects may be "immunological hyperreactors." However, other possible factors such as variation in past experience with streptococcal antigens must be considered in the interpretation of such findings, and the data from the delayed treatment study,[24] mentioned previously, indicate that rheumatic fever can be prevented in spite of considerable antibody production. Certainly, rheumatic fever patients do not appear to be "hyperreactors" in general, as they respond in a fashion similar to nonrheumatic individuals when challenged with nonstreptococcal antigens.[40,41]

The quantitative aspects of antibody formation have not been as well studied in acute glomerulonephritis as they have in acute rheumatic fever. Nevertheless, the low titers of serum complement[42] and the latent period have been adduced as proof of an antigen-antibody mechanism in this disease.

Since it is a crucial point in any antigen-antibody theory, the latent period which is present in both of these diseases deserves further consideration. It is interesting to note that the average latent period is shorter in acute glomerulonephritis (ten days) than it is in acute rheumatic fever (eighteen days).[43] The meaning of this observation is not clear. It may simply mean that a more sensitive clinical indicator of disease (hematuria) is present in acute nephritis, and, therefore, the disease is recognized earlier. On the contrary, it may indicate some fundamental difference in the pathogenesis of these diseases. Just what this difference might be is not immediately apparent. The shorter latent period in acute nephritis suggests that it is more apt than rheumatic fever to be the result of direct action of some streptococcal product, yet the similarity of the latent period of acute nephritis to that of serum sickness suggests that it is more likely than rheumatic fever to be related to antibody mechanism.[43] Possibly the two complications may involve different antigen-antibody systems, since it is known that the time of antibody response may vary with different streptococcal antigens.

The unusual susceptibility of rheumatic subjects to recurrence after the acquisition of a new streptococcal infection, over 50 per cent in some series,[30] is not only the basis for many prophylactic programs, but also supports the theory that an antigen-antibody mechanism is important in the pathogenesis of this disease. The question of recurrences in relation to kidney disease is confusing. Exacerbation of the symptoms of chronic nephritis by streptococcal infection has been reported,[44] but the relationship of this disease to acute glomerulonephritis is not clear. Most patients with chronic glomerulonephritis give no history of an episode of acute glomerulonephritis, whereas most patients, especially children, with acute glomerulonephritis do not develop chronic kidney disease.[45] Rammelkamp[43] has recently suggested that the two kidney diseases may be distinct and unrelated entities and has presented preliminary evidence supporting this thesis. Final resolution of this problem awaits long-term follow-up studies of patients with acute glomerulonephritis following known streptococcal infections.

Immunologic reactions, unrelated to the amount or type of circulating antibody, can be produced with various streptococcal products. Thus, the existence of bacterial hypersensitivity of the delayed type has been demonstrated in humans with heat-killed streptococci and with a number of streptococcal products.[46] The nonavailability of purified preparations of streptococcal products has made studies of these reactions difficult, and the possible quantitative and qualitative differences in rheumatic and nonrheumatic subjects have not been thoroughly explored. Recent interest in this subject has been stimulated by the demonstration that this generalized cutaneous reactivity to streptococcal products can be passively transferred by cells or cellular constituents.[46]

Thus, the antigen-antibody theory remains a fascinating hypothesis, but definite proof of its role in the pathogenesis of acute rheumatic fever or acute nephritis has not been produced. Furthermore, the possible importance of bacterial hypersensitivity is not known.

Atwater[47] and Rosenau[48] were among the first to point out a correlation of the annual death rates for rheumatic fever and streptococcal infections. The epidemiologic association of streptococcal infections with acute rheumatic fever and acute glomerulonephritis has now been confirmed by the reports of a number of epidemics.[16–19,49] Moreover, it has become obvious that many of the factors, such as season, crowding, and age, which seem to influence the incidence of acute rheumatic fever and acute glomerulonephritis, may do so indirectly by their influence on the incidence of streptococcal infections.[50]

The factor of age is of particular interest since much stress has been laid on the "peculiar susceptibility" of certain age groups to rheumatic fever and acute glomerulonephritis. Thus, initial attacks of rheumatic fever are rare in the infant, infrequent in the preschool child, common in the school child, and unusual in the adult.[51] Attacks of acute glomerulonephritis show a similar age distribution, although exceptions[45] are often seen in family outbreaks. Some cases of acute rheumatic fever may be missed in young infants because of difficulties of diagnosis in this age group, but most authorities have ascribed its infrequency in infants to some mysterious immaturity of the tissues. Others have emphasized the necessity for the host to be sensitized by repeated streptococcal infections.[52] Scant attention has been paid to a less complex explanation—the apparent infrequency of group A streptococcal infections in young infants. Obviously, this might be a critical factor *per se*. Adequate data are not available on this point as it is difficult to define streptococcal infection or acute rheumatic fever in this age group, and some reports have included as infection instances where infants were found to harbor non-group A or nontypeable streptococci.[52] In this regard, it is interesting to note that an easily recognized streptococcal infection, scarlet fever, has an age incidence which closely resembles that of initial attacks of acute rheumatic fever, reaching a peak at 6 years of age and gradually tapering off during the subsequent years of childhood.[53] The relative infrequency of rheumatic fever in the adult can most readily be explained by this waning incidence of streptococcal infections. The fact that adults are still susceptible has been demonstrated many times when they have been subjected to an increased risk of acquiring streptococcal infections. This occurs when young adults are exposed to epidemic streptococcal disease in the service, or when adults move from a climate where streptococcal infections are rare to one where they are common.[54] Little is known about the factors which influence the age distribution of streptococcal infections, but, since the distribution is similar to that of other respiratory infections,[55] common factors might be suspected to be important. Recognition that the incidence of streptococcal infections and, hence, nonsuppurative complications, varies with age is important in designing programs of control. Thus, the adult with rheumatic fever is less likely to acquire a streptococcal infection and thereby develop a recurrence than the child. Consequently, long-term continuous prophylaxis is not as imperative in the adult, unless he is subjected to special situations of increased risk, such as may occur when he enters the Armed Forces.

A comparison of the epidemiologic features of acute rheumatic fever and acute glomerulonephritis reveals some striking differences, which Rammelkamp and associates[56] have recently shown to be important leads in the attempt to unravel the pathogenesis of this latter disease. The attack rate of rheumatic fever appears to bear a fairly constant relationship to the incidence of group A streptococcal infections. Under well-defined conditions, approximately 3 per cent of individuals infected with group A streptococci develop initial attacks of rheumatic fever. This relationship seems to hold regardless of the geographic area, the time of the infection in relation to the epidemic curve, the clinical manifestations of streptococcal disease, or the serologic type of the group A streptococcus.[50] In contrast, the incidence of acute glomerulonephritis after known streptococcal infections seems to be var-

iable. Thus, acute nephritis is nonexistent in some epidemics of streptococcal infection and quite common in others.[49] Furthermore, attacks of rheumatic fever tend to occur at different times or in different generations of the same family, whereas several members of one family may develop acute nephritis simultaneously. As pointed out by Rammelkamp and Weaver[49] these differences suggest that strains of group A streptococci may vary in their capacity to produce renal damage. These workers have further demonstrated that types 12 and 4 are especially apt to be nephritogenic. This observation is particularly significant, since it suggests that these nephritogenic strains have some biologic peculiarity which is related to their ability to induce kidney disease. The nature of this biologic peculiarity, if it exists, has not been identified. The realization that certain strains and probably only a few strains of streptococci are nephritogenic explains why recurrences of acute glomerulonephritis are so rare, whereas recurrences of acute rheumatic fever are common. Since immunity to streptococcal infections is type-specific,[22] a patient who is convalescent from acute glomerulonephritis would be expected to be immune to the type of streptococcus which had precipitated the attack, and it would be unlikely that he might be subsequently infected with one of the few remaining prevalent nephritogenic types. This is an important point to keep in mind in making recommendations for the control of streptococcal infections and their sequelae. It indicates that continuous prophylaxis is probably unnecessary in the patient who has recovered from acute glomerulonephritis.

Although the identification of nephritogenic strains has done much to explain certain dissimilarities in the epidemiology of acute rheumatic fever and acute glomerulonephritis, it does not appear to clarify all of these differences. In particular, it does not suggest why acute nephritis occurs more often in males than in females, whereas there is no consistent sex difference in acute rheumatic fever.[8] Also, it does not indicate why rheumatic fever, as well as scarlet fever, is more frequently reported in the northern than the southern portions of North America, whereas acute nephritis is apparently as common in the South as in the North.[57] Furthermore, it does not explain the clinical observation that acute glomerulonephritis is often associated with skin or wound infections, whereas rheumatic fever rarely follows this type of infection.[8,9] The significance of skin infections in the pathogenesis of acute nephritis is not entirely clear as cultures of the skin may be misleading. Thus, in patients with streptococcal skin infections, the organism can usually be cultured from the upper respiratory tract as well as the skin lesion, and, conversely, streptococci can often be cultured from apparently normal skin in patients with obvious streptococcal pharyngitis. Nevertheless, the relationship of acute nephritis to pyoderma is certain in the minds of many clinicians, and it is interesting to speculate that some strains of streptococci might have a propensity for the skin as well as the kidney. Moreover, one might speculate that, if streptococcal skin infections are more common in the South, as they may well be in certain population groups, then they may tend to elevate the incidence of acute glomerulonephritis to a level similar to that seen in the North where streptococcal infections of the respiratory tract occur more frequently.

Attempts to produce in the experimental animal a disease resembling acute rheumatic fever or acute glomerulonephritis have been less fruitful than efforts to elucidate the association of streptococcal infection and their sequelae on clinical, bacteriologic, serologic, and epidemiologic grounds. Early endeavors to produce an experimental model for rheumatic fever by injection of streptococci of various kinds into animals failed.[58] Experimental pathologists were soon influenced by the concept of allergy suggested by Schick[59] and by the clinical resemblance of rheumatic fever to serum sickness as pointed out by Weintraub.[60] Subsequent attempts to draw an analogy betwen rheumatic fever and serum disease were stimulated by the work of Rich[61] who injected rabbits with foreign serum and produced heart lesions resembling those of periarteritis nodosa.

Recently, Murphy and Swift,[62] after repeated focal infections with group A streptococci of several types, have produced fresh lesions of myofiber Aschoff-body type in a few of many rabbits. Although it is difficult and sometimes hazardous to equate an experimental model with a human disease, it is of interest to note that, like the human disease, only a few of the rabbits were affected. This suggests that a host factor may be important. This model also gives some support to the theory that multiple infections with different types may be important in the pathogenesis of rheumatic fever. Another intriguing experimental model has been produced by Thomas and associates.[63] In their studies of the Shwartzman reaction, these investigators have shown that maximum systemic infections with group A streptococci followed by an intravenous injection of gram negative endotoxin produces in rabbits the characteristic le-

sions of the generalized Shwartzman reaction, including myofiber necrosis in the myocardium, but under certain optimum conditions of dosage and of timing, accumulation of fibrinoid material in the walls of coronary arteries can be produced in half of the animals. The authors wisely decline to speculate on the significance of the resemblance of these lesions to those of rheumatic fever and related diseases.

In the experimental kidney disease produced in animals by injection of nephrotoxic serum, lesions resembling those of acute nephritis have been reported in some instances.[64] The demonstration that some types of streptococci are nephritogenic has enlivened interest in this problem, as it may not only explain why previous efforts have failed but suggests new lines of approach. Reed and Matheson[65] have reported the development of hematuria and hypertension in rabbits after injection of type 12 streptococci or supernatant fluid from broth cultures of these organisms, but other attempts to produce a satisfactory homologue of acute glomerulonephritis by the use of nephritogenic streptococci or streptococcal products have so far been unsuccessful.[66,67]

From the accumulated evidence, briefly reviewed here, few investigators doubt the importance of group A streptococcal infections in the etiology of acute rheumatic fever or acute glomerulonephritis, but some skepticism remains as to whether these diseases are invariably preceded by a streptococcal infection. This question arises when an occasional patient with one of these diseases fails to show clinical, bacteriologic, or serologic evidence of such an infection. As has been pointed out, these exceptions are to be expected since not every patient convalescent from streptococcal infection presents such evidence. However, some skepticism continues to be fostered by reports from reliable investigators that fractures and surgical operations occasionally seem to precipitate recurrences of acute rheumatic fever[68] and, more recently, by the observation that some evidence of rheumatic activity may develop after mitral commissurotomy.[69] Although it is possible that a concomitant streptococcal infection might have been missed or that latent infection may be incited by such procedures, no completely adequate explanation is apparent at this time. Those who would implicate the adrenals in the pathogenesis of rheumatic fever might be attracted by the stress of injury or surgery, whereas the frequency of recurrence after operations on affected valves is intriguing to those who postulate that streptococci, in some form or another, or their products might reach the heart during the development of rheumatic fever. In the case of acute nephritis, other infectious agents have been reported to produce, on occasion, kidney lesions morphologically similar to those seen in the hemorrhagic nephritis following streptococcal infection.[70] The clinician may be less inclined than the pathologist to recognize this as the same disease. It seems likely that as we become more adept at separating the various clinical and pathologic pictures of kidney disease on the basis of etiology and pathogenesis, this problem will disappear.

The emphasis which has been placed in this discussion on the role of infection in the pathogenesis of acute rheumatic fever and acute glomerulonephritis is not meant to imply that host factors are irrelevant or unimportant. However, in the light of our present knowledge and in the framework of present-day mores, the more practical attack to the problem of prevention of these diseases is from the standpoint of infection rather than from the standpoint of the host. Although the variation in host response to streptococcal infection is well recognized, it is poorly understood. Whether this variation in response is inherited, acquired by previous conditioning, or indeed is due to some peculiarity of the infection or of the infectious agent itself is not known. Reference has already been made to the recent evidence that differences in infecting strains may be of importance in the pathogenesis of acute glomerulonephritis and that location of infection has been considered significant by some clinicians. Attempts to elucidate the pathogenesis of rheumatic fever in terms of infecting type of streptococcus, clinical peculiarities of the infection, or general hyperreactivity of the infected host have failed.

Considerable attention has been paid to the familial occurrence of rheumatic fever and acute glomerulonephritis, but again genetic and environmental factors are difficult to separate. In this regard, it is interesting to observe that for years a similar state of confusion existed in regard to tuberculosis. As has been pointed out previously, the tendency of acute nephritis to develop simultaneously in several members of a family suggests the importance of environmental or bacterial factors, whereas the tendency of rheumatic fever to occur at different times in the same family or in different generations of the same family suggests the importance of inherited factors. Evidence of the role of genetic factors in the etiology of rheumatic fever has been collected by Wilson[51] who tends to disregard the role of streptococcal infections. The

nature of the genetic defect, if such exists, has not been defined, and most investigators strongly doubt that it expresses itself as clinical rheumatic fever in the absence of streptococcal infection. Recently the suggestion has been made that individuals from rheumatic families may acquire streptococcal infections more readily than those from nonrheumatic families.[71] This thesis has not been established, but the possibility is intriguing in attempting to explain the familial occurrence of rheumatic fever. Preliminary studies at the Streptococcal Disease Laboratory[72] indicate that, after known streptococcal infections in young adults, the antistreptolysin 0 response and the attack rate for rheumatic fever are no higher among individuals with a positive family history for rheumatic fever than among individuals with a negative family history for rheumatic fever. However, in dealing with a young adult population such as this, many of the susceptible members of the rheumatic families may have been weeded out by previous experience with streptococci which resulted in earlier attacks of rheumatic fever. Further studies are needed among children of rheumatic and nonrheumatic families in order to define both the risk of acquiring streptococcal infections and the risk of developing an attack of rheumatic fever after infection occurs. Such studies should include careful serial bacteriologic and serologic as well as genetic and clinical observations. In addition, much information of both practical and theoretic value might be obtained from a study of continuous prophylaxis among siblings of rheumatic fever patients.

In summary, attacks of acute rheumatic fever and acute glomerulonephritis are regularly preceded by group A streptococcal infections, although such infections are sometimes mild or not apparent. The mechanism by which these complications develop and the possible role of genetic and of other host factors, including age, are not clear. Formerly, emphasis was placed on exaggerated antibody responses in patients developing acute rheumatic fever, but more recent evidence suggests the importance of the persistence of streptococci in body tissues in the pathogenesis of this disease. Recent studies have indicated the significance of strain variation in the etiology of acute glomerulonephritis. Although knowledge of the role of infection in these diseases is incomplete, such knowledge has led to the development of practical programs of control, and the demonstrated success of these programs has, in turn, confirmed and strengthened the position of group A streptococcal infections in the etiology of these diseases.

THE RECOGNITION OF INFECTION

One of the most pressing needs in the control of streptococcal infections and their sequelae is for better means of recognition of existing disease, and for more widespread utilization of those means which are available. Much has been written about the diagnosis of acute rheumatic fever and acute glomerulonephritis, but too little attention has been paid to the diagnosis of streptococcal infections of the respiratory tract, which frequently go unrecognized, disregarded, or misdiagnosed. It is elemental that the success of any control program based on the treatment of streptococcal infections is ultimately dependent upon their recognition.

When acute streptococcal pharyngitis or tonsillitis occurs in its typical form, the diagnosis is rarely missed. In fact, the error is probably more often made in the other direction. That is, many exudative and nonexudative lesions of the pharynx and tonsil are casually called "strep throat" although they are frequently not of streptococcal etiology. This is particularly true in children, in whom nonstreptococcal exudative pharyngitis is especially common.

As with most infectious diseases, the presence of an epidemic makes the decision on the individual case less difficult. Sporadic cases are less easily recognized and often require laboratory confirmation before a definite diagnosis can be made.

In its typical form,[21,73–74] streptococcal pharyngitis or tonsillitis has a fairly abrupt onset. The patient can ordinarily time the onset within definite limits of one or two hours. Furthermore, the patient rarely gives a history of several days or a week of rhinitis which then suddenly or gradually develops into streptococcal pharyngitis. This is not surprising, since there is little evidence to support the popular opinion that viral infections of the upper respiratory tract predispose to streptococcal pharyngitis.

The first symptom may be headache, sore throat, or a feverish feeling. True shaking chills are rare, but chilly sensations are common. Convulsions may occur in children. Rarely, the patient may present symptoms of stupor or delirium. Children are particularly apt to complain of abdominal pain, nausea, or vomiting.

The cardinal symptom is sore throat as it points out the site of infection. This is usually described as more than a mere tickle in the throat, a rawness or dryness on awakening, or an irritation as may occur from a postnasal drip. Most patients indicate that they have definite pain when swallowing, and, in young children, this may be suggested by their refusal to swallow food.

Fever is characteristic. It may be either low-grade or quite high but frequently ranges between 101 and 104° F.

In the presence of cough or hoarseness, some other etiology should be suspected as bronchitis and laryngitis rarely accompany streptococcal pharyngitis.

On physical examination, the patient with typical streptococcal infection of the upper respiratory tract exhibits findings in the tonsils or pharynx, in the anterior cervical lymph nodes, and occasionally in the skin.

"Injection" of the throat has very little meaning and even redness is difficult to evaluate as it may vary with the light source used and the amount of edema present. Exudate is characteristic of streptococcal infection of the upper respiratory tract. If it is not present at the time of first examination of the patient, it often appears within a day or two. The exudative lesions are usually bilateral and present on the tonsils, in the tonsillar fossae, or on the lymphoid tissue of the posterior pharynx. They are ordinarily discrete and patchy, although they may be pinpoint or confluent. Exudate must be carefully differentiated from food and debris in the tonsillar crypts.

The presence of exudate does not establish a streptococcal etiology as it must be distinguished from the lesions of diphtheria, infectious mononucleosis, herpes, and Vincent's angina and from exudative lesions of the throat which occur with well-recognized infectious diseases such as rubella. It is particularly difficult to differentiate streptococcal exudative tonsillitis and pharyngitis from the so-called nonstreptococcal exudative tonsillitis and pharyngitis which is presumably viral in etiology.[75] Antibodies to an agent which is cytopathogenic in HeLa cell cultures have recently been demonstrated in patients with this disease.[76] This disease is especially prevalent in children, and epidemics are most apt to occur during the summer months. No sharp clinical differentiation can be made between this disease and streptococcal infection of the upper respiratory tract. In general, nonstreptococcal exudative tonsillitis has a less abrupt onset and produces less local and less systemic reaction. Exudate is more likely to be pinpoint or discrete rather than discrete or confluent as is more often seen in streptococcal tonsillitis. The white count and regional lymph nodes are less regularly affected than in streptococcal infections of the throat.

The anterior cervical lymph nodes are usually tender in streptococcal infections. Tenderness is a more significant sign than size, for many normal children may present cervical nodes which are quite large, especially by adult standards.

If a scarlatinal rash is present, the diagnosis is obvious as other infectious diseases rarely produce skin rashes which resemble that of scarlet fever. A scarlet-like rash is said to accompany staphylococcal infections on occasion.[77] Atropine or ephedrine poisoning or other drug reactions may be confused with scarlet fever at times. In general, however, the appearance of a scarlatinal rash is pathognomonic of streptococcal infection.

Although a typical rash is the most reliable aid in making a clinical diagnosis of streptococcal infection, it is often absent. Indeed, because of the striking picture of the rash, clinicians and public health officials have tended to regard scarlet fever as a disease which is quite different from other streptococcal infections. The persistence of this attitude is unfortunate as it has resulted in the continuance of public health laws which emphasize the rash and fail to recognize that nowadays streptococcal infections more often occur in less obvious forms.

The occurrence of typical signs and symptoms usually arouses the suspicion of streptococcal infection, but many streptococcal infections presenting subclinical or atypical pictures escape detection.[10,78] Such infections are a major impediment in planning programs of control. For most infectious diseases, the importance of these unrecognized infections lies largely in their danger as a source of infection for others. In streptococcal disease, these "missed infections" assume additional significance for they are responsible for a large share of the late and more important sequelae.

The percentage of streptococcal infections which go unrecognized is difficult to estimate accurately. Among adults, in whom the infection tends to be more typical, and in military populations alerted to the prevalence of epidemic streptococcal disease, approximately 40 per cent of such infections are either not brought to the attention of a physician or are diagnosed clinically as nonbacterial respiratory infection.[10] In young children, in whom streptococcal infection is more apt to be atypical and in populations where infection tends to be endemic rather than epidemic, the proportion of unrecognized streptococcal infections is undoubtedly higher.

Subclinical infections can only be recognized by cultural and serologic investigations. Their existence should be suspected whenever frank cases of streptococcal infection appear in a family or in other population groups, such as or-

phanages, schools, hospital wards, or barracks. These infections may be detected by a culture survey of the family or other population group.

Atypical infections[10,78] may appear as an ordinary nasopharyngitis. Symptoms and signs relative to the throat may be minimum or absent. Frequently, complaints of sore throat can only be elicited by direct questioning, and the degree of inflammation would not attract attention on routine examination.

Powers and Boisvert[79] have stressed the importance of age in conditioning the response of an individual to streptococcal infection. They have compared the manifestations of streptococcal infections at various ages with those of tuberculosis and have coined the term "streptococcosis" to emphasize this resemblance. When used correctly, this term applies to the broad spectrum of clinical varieties of streptococcal infection and not to the specific atypical form of infancy and early childhood.

According to Powers and Boisvert,[79] young infants with their first streptococcal infection present a clinical picture strikingly different from that observed in older children and adults. The very youngest infants, under 6 months, may be completely asymptomatic or may show irregular low-grade fever, anorexia, vomiting, or diarrhea for a week or less with a persisting thin mucoserous discharge from the nose and excoriation and crusting around the external nares. Somewhat older infants and children, those between 6 months and 3 years, are described as more severely ill. The onset is insidious and the early manifestations are those of coryza, fever, loss of appetite or vomiting, postnasal discharge, and nonexudative inflammation of the pharynx. Fever is moderate. It becomes low grade after a few days and often lasts four to eight weeks. During this period the infant may lose weight and may appear pale, unhappy, and querulous. Enlargement of the cervical nodes and catarrhal otitis occur regularly, and suppurative complications frequently develop.

Although these atypical infections appear to occur most often in young infants,[52,79] it is recognized that streptococcal infections resembling nasopharyngitis may also occur in older groups.[10,78] The exact relative incidence of these infections in various age groups has not been established. It is particularly difficult to determine the incidence of these infections in young infants. With minimum clinical manifestations and poor or questionable antibody responses, it is almost impossible to be sure that such infants are actually infected in the ordinary sense of the word, although hemolytic streptococci may be cultured from the nose or throat. This is especially true since a considerable number of the strains isolated are either not group A or cannot be typed.[52]

A high index of suspicion is needed to detect atypical streptococcal infections, but the alert physician looks askance at a persistent nasal discharge with excoriation of the external nares in an infant or at ordinary nasopharyngitis in a child whose siblings have typical streptococcal disease.

Even in the presence of exudative tonsillitis, however, a definite diagnosis of streptococcal infection is impossible on clinical grounds alone. Therefore, laboratory confirmation should be obtained whenever possible. Helpful laboratory procedures include total white count, culture of the throat and nose, and antistreptolysin 0 titers.

The white blood count is perhaps the simplest and most readily obtainable of these laboratory aids. Adults with streptococcal infections usually show total counts of over 10,000, whereas counts of more than 12,000 are probably significant in children.[52,80] A moderately elevated count may occur with nonbacterial infections of the throat, but a low count is unusual in infections of streptococcal etiology.

Smears of the throat are of no value as hemolytic streptococci are impossible to distinguish from other varieties.

In substantiating a clinical impression of streptococcal infection, cultures are essential. Unfortunately, facilities for obtaining cultures for hemolytic streptococci are not always readily available, and many hospital and municipal laboratories are still geared toward multiple serologic tests for syphilis and the identification of diphtheria organisms rather than toward the reliable identification of hemolytic streptococci. If cultures are properly done, hemolytic streptococci can be recovered from 90 to 95 per cent of patients on a single culture, and 100 per cent can be approached if multiple cultures are taken.[80,81]

The technic of obtaining the culture is important. The cotton swab should be firmly rubbed over both tonsillar areas and the posterior pharynx and should be inoculated onto blood agar within one hour.

Hemolytic streptococci grow well on agar base with added blood from a number of animal species, but differentiation of beta-hemolytic from alpha (green) streptococci is difficult on some types of blood. Human blood, which is used in many routine laboratories, is particularly unsatisfactory. "False positive" results may be obtained on human or horse blood agar. Rabbit

blood agar appears to be satisfactory, but the best medium to use is sheep blood agar as hemolytic and green colonies are ordinarily easy to distinguish on this medium. Most group A streptococci produce unmistakably clear hemolysis on sheep blood agar. Conversely, non-group A streptococci — strains frequently not pathogenic for man — are more likely to produce green or partial hemolysis on sheep blood agar than on other types of blood agar.[82] An added advantage of sheep blood agar is that Hemophilus hemolyticus which may be confused with the hemolytic streptococcus either fails to grow or grows poorly on this medium.[83]

In preparing blood agar plates, it is important to streak with a platinum loop in order to obtain well isolated colonies which are not obscured by growth from other organisms. Subsurface as well as surface hemolysis should be studied as some strains of group A streptococci produce very green hemolysis on surface streaking but typically clear hemolysis around subsurface growth. In studying subsurface hemolysis, the preparation of pour plates is an unnecessary chore. Information on the type of subsurface hemolysis can be obtained on routine original plates by making a simple stab into the medium with the platinum loop.[82]

Since hemolytic streptococci can be found in the nose or throat under a variety of circumstances,[22] their identification on culture is by no means unequivocal evidence of current infection with these organisms. Thus, hemolytic streptococci may persist for months in the throat and may bear no relationship to the current respiratory infection. Also hemolytic streptococci may appear as transients, particularly in the nose and less often in the throat. In such instances, the streptococci probably should not be considered to be producing infection inasmuch as they do not appear to multiply or become established residents and provoke no detectable clinical or immunologic response in the host. Finally, hemolytic streptococci which are non-group A may be present in the upper respiratory tract. Streptococci of groups C and G are considered to be occasionally pathogenic for man,[84] but they apparently do not result in either acute rheumatic fever or acute glomerulonephritis. Because of the prevalence of these presumably nonpathogenic strains, it is desirable to identify serologically all hemolytic streptococci isolated from the nose or throat.

From a practical standpoint, some indication of the significance of finding hemolytic streptococci on cultures from the upper respiratory tract may be gained from rough quantitation of the number of colonies present. Cultures showing only a few hemolytic streptococci are more often obtained from chronic carriers, or occasionally from patients with incipient infection, rather than from patients with well-established current infection. Conversely, cultures with a predominant growth of hemolytic streptococci are more apt to be obtained from patients with acute infection than from chronic carriers.[20] Also the location of streptococci may be a helpful clinical guide. Approximately two-thirds of patients with acute streptococcal infections harbor hemolytic streptococci in the nose as well as the throat, whereas the organism seldom persists in the nose beyond the acute stage except in the presence of some complication such as chronic sinusitis.[85] However, the presence of streptococci in the nose does not always indicate infection, as they may be found in small numbers as inactive transients.[22]

The most reliable laboratory evidence that infection with hemolytic streptococci has occurred is the demonstration of a serologic response. A two-dilution increment of antistreptolysin 0 is dependable evidence that infection has occurred. However, certain factors limit the practical usefulness of this test as an aid in the diagnosis of streptococcal infection. Since an appreciable rise does not regularly occur until several weeks after the initiation of infection, the test is of no immediate value in establishing a clinical diagnosis. Moreover, if antibiotics are administered, the serologic response may be suppressed.[21] Thus, to most practicing clinicians, antistreptolysin 0 titers are more useful in supporting the impression of acute rheumatic fever or acute glomerulonephritis than in differentiating acute respiratory infections.

To summarize, streptococcal infections of the upper respiratory tract may occur in several forms. Typical infections have a sudden onset with fever, definite pain when swallowing, exudative lesions of the tonsils or pharynx, and tender cervical nodes. Only in the presence of a scarlatinal rash can an unequivocal diagnosis of streptococcal infection be made on clinical grounds alone. Atypical infections may appear as a mild nasopharyngitis. These are thought to be especially common in young infants where the course may be more chronic and the chief clinical manifestation is often a persistent nasal discharge with excoriation about the external nares. Atypical infections may also occur in adults, and completely asymptomatic infections are found in all age groups. The proportion of infections which are either mild, atypical, or asymptomatic is not well established. In young

adults, they account for perhaps 40 per cent of infections and in infants, they are thought to occur even more frequently. Laboratory studies are helpful in confirming the diagnosis in patients with typical findings and in suggesting or establishing the diagnosis in atypical or subclinical infections. A leukocytosis of over 10,000 in adults and over 12,000 in children is characteristic. In acute streptococcal infections, cultures of the nose and throat ordinarily reveal hemolytic streptococci in large numbers. In chronic carriers with an intercurrent nonstreptococcal infection, the organism is less likely to be present in the nose and the number of colonies on throat culture is more apt to be few. Sheep blood agar is the most reliable medium for the identification of hemolytic streptococci. When streaking the culture, a stab should be made into the agar as some group A streptococci are hemolytic on subsurface growth only. A rise in streptococcal antibodies, such as antistreptolysin O, is the most dependable indication that infection has occurred. The clinical value of such antibody tests is limited because the diagnosis can only be confirmed in retrospect and because treatment with antibiotics may inhibit antibody formation.

THE MANAGEMENT OF INFECTION

In a short-termed, self-limited infection, such as streptococcal pharyngitis or tonsillitis, the possibilities of altering the course of the acute disease are necessarily restricted. The patient has often reached or is nearing the symptomatic turning point in his illness before he presents himself for treatment. Therefore, the physician who blindly follows a group of patients with streptococcal infection — that is, without knowledge of which individuals are and which are not receiving antibiotics — finds it difficult, if not impossible, to distinguish the treated from the untreated individuals on the basis of clinical findings alone. Only by careful comparison of large groups of patients can differences in the duration of symptomatology and physical signs be demonstrated. Unless treatment is started soon after the onset of symptoms — within less than twenty-four hours — these differences are not dramatic, and the duration of the various manifestations of illness is rarely shortened by more than one day.[80,81]

Sulfadiazine may result in a slight reduction of the frequency of sore throat and in the height and duration of fever, but from the standpoint of practical therapeutics no beneficial effect on the acute illness can be demonstrated.[86] Comparison of the effects of penicillin, chlortetracycline, and oxytetracycline on the clinical course of the acute illness shows some differences in regard to certain manifestations, but no one drug is consistently most effective.[80,81] The definite tendency of the tetracyclines to produce gastrointestinal symptomatology might make them less desirable than penicillin from the standpoint of the patient's comfort. Haight [87] has reported that Erythromycin is as effective as penicillin in shortening the clinical features of scarlet fever. He also found fewer skin rashes with Erythromycin, although the incidence of skin rashes attributed to penicillin in this study is considerably higher than in other reported series.[88–91]

Thus, in most instances, no striking alteration of the clinical course of streptococcal illness can be achieved by the administration of antibiotics, and, aside from certain differences in toxicity, there appears to be no obvious choice among a number of available agents. Hence, the justification for the routine use of antibiotic therapy and the indications for the selection of a particular antibiotic must be sought on other grounds.

There are two cogent reasons for the adequate treatment of streptococcal infections: (1) to prevent spread of infection to other individuals, and (2) to reduce the incidence of complications.

Human reservoirs of streptococci are important sources of secondary infection and individuals who have recently acquired streptococci in the nose or throat are especially apt to transmit the infective agent to others with whom they are in contact.[22] This is dramatically illustrated in family episodes, school outbreaks, and military epidemics where it is not unusual for more than half of the group to experience either clinical or subclinical infection. Therefore, it would seem important to eliminate the infecting organism from the upper respiratory tract in order to minimize such spread. Sulfadiazine suppresses the growth of group A streptococci and may thereby temporarily reduce the risk of transmission of infection. However, when the drug is discontinued, the infecting organism can again be recovered from the nasopharynx.[86,92] In contrast, therapy with certain antibiotics often eradicates the infecting organism so that group A streptococci of the infecting type cannot be recovered in cultures of the throat taken after termination of the drug.[21] Penicillin seems to be more effective than the tetracyclines in eradicating group A streptococci from the throat.[81] Erythromycin is apparently equally as effective as penicillin in this regard.[87]

In attempting to eradicate the infecting organism, the dose of penicillin, the preparation

used, and the manner in which it is administered do not seem to be as important as the duration of treatment. If penicillin is given in such a fashion as to maintain levels for ten days, the infecting organism will be eradicated in approximately 90 per cent of patients with acute infection. Shorter courses do not prove as effective in ridding the streptococcus from the throat.[21] The failure of treatment which is discontinued after several days is probably related to the fact that penicillin is ordinarily bactericidal only to actively multiplying organisms. Perhaps a number of days is required for all organisms in a bacterial population to pass through a stage when they will be most subject to this bactericidal action. It is interesting to observe that group A streptococci are also more difficult to eradicate from the throats of carriers than from the throats of individuals with active infection.[88] This is probably also related to the slow rate of metabolism and growth of orgainsms in carriers. Eagle[93] has presented interesting data in the experimental animal supporting these clinical observations.

It appears that suppurative complications, such as otitis media, sinusitis, and peritonsillar abscess, can be prevented by the administration of one of the sulfonamides or any of the antibiotics previously mentioned. Most of the controlled studies, however, have been done in young adults in whom suppurative complications are unusual.[80,81]

It is now well established that adequate treatment of acute streptococcal infections also prevents nonsuppurative complications. An imposing body of evidence is available in regard to acute rheumatic fever,[21,94–96] and more limited information is available in regard to acute glomerulonephritis.[20,43] Adequate treatment with penicillin[21] can reduce the incidence of acute rheumatic fever after known streptococcal infections by more than 90 per cent. Whether penicillin treatment of acute streptococcal infections prevents rheumatic carditis has not been established.[10] Since rheumatic heart disease may develop insidiously many years after the last recognizable episode of rheumatic activity,[97] this is an extremely complex and difficult question to answer.

For maximum prevention of acute rheumatic fever, it should be emphasized that the treatment must be adequate. Again adequate treatment seems to be best and most easily defined in terms of eradication of the infecting streptococcus.[20,98] Treatment of acute streptococcal infections with cortisone reduces neither the prevalence of cultures positive for group A streptococci nor the attack rate for acute rheumatic fever.[99] Sulfadiazine merely temporarily inhibits the growth of the organism and does not reduce the incidence of acute rheumatic fever.[86] Likewise, chlortetracycline and oxytetracycline seem to be less effective than penicillin in eradicating the infecting bacteria, and are also less effective than penicillin in preventing acute rheumatic fever.[20,96] These drugs should be reserved for treating streptococcal infections in individuals sensitive to penicillin. Currently available information on Erythromycin is limited, but it appears to be as effective as penicillin in eradicating group A streptococci.[87] In order to eradicate the infecting organism, the drug must not only be bactericidal but must also be exhibited for a sufficient length of time. As has been pointed out previously, regimens in which penicillin is administered or maintained in the body for ten days appear to be reliable.

A number of preparations of penicillin have been used. Penicillin troches and sprays are useless as they cannot be relied upon either to eradicate the streptococcus or to reduce the incidence of complications. The most extensive studies have been done with crystalline procaine penicillin G in sesame or peanut oil containing 2 per cent aluminum monostearate, administered intramuscularly.[21] An effective dosage schedule with this preparation appears to be 300,000 units statim, 300,000 units at forty-eight hours, and 600,000 units at ninety-six hours. Daily intramuscular injections of 600,000 units of crystalline procaine penicillin G have also been employed.[81] For optimum therapy with this preparation, treatment should probably be continued for ten days although, in the study cited, 5 daily injections appeared to eradicate the infecting organism in approximately 90 per cent of patients as determined by a single culture at three weeks.

Well-controlled studies employing oral penicillin for the treatment of acute streptococcal infections are few, but the reports of Massel and associates.[94,95] suggest that the incidence of acute rheumatic fever can be reduced by such treatment. They employed buffered tablets of sodium or procaine penicillin G in doses of 200,000 units 5 times daily or 300,000 units 3 times daily for ten days. However, the dosage required to eradicate the infecting organism is not well established, and the relative effectiveness compared to intramuscular administration is not known.

Because duration of treatment appears to be important, considerable recent interest has centered around the use of long-acting preparations of penicillin. DBED penicillin (N, N' dibenzyl-

ethylenediamine dipenicillin G) is a relatively insoluble salt which is currently popular as a repository preparation of penicillin. A single intramuscular injection of 1,250,000 units of this preparation has been reported by Stollerman and Rusoff[100] to produce detectable blood levels of penicillin in all of 16 patients at twenty-one days and in 12 of the 16 patients at twenty-eight days. A recent report from the Streptococcal Disease Laboratory[98] indicates that a single injection of either 600,000 or 1,200,000 units of DBED penicillin is strikingly effective in eradicating the infecting streptococcus. No nonsuppurative complications developed in 257 patients treated in this manner, whereas 2 cases of acute rheumatic fever and 1 case of acute nephritis developed in 109 untreated controls.

Although DBED penicillin appears to have the advantage of assuring effective treatment with only one visit to the doctor, it also has certain disadvantages. It appears to be considerably more painful than other forms of injectable penicillin.[98,100,101] Whereas toxicity has not been considered a problem in reports dealing with children,[100,101] the incidence of reaction may be appreciably higher in young adults[98] than the approximately 1 per cent encountered with other forms of penicillin.[88–91] Thus, in 2 as yet unreported series,[20,102] manifestations of serum sickness, such as urticaria, angioneurotic edema, and joint symptoms occurred in from 2 to 5 per cent of normal young adults after a single injection of DBED penicillin.

Because late treatment also reduces the incidence of nonsuppurative complications,[24] the physician should not hesitate to start treatment in such instances, although the patient has symptomatically recovered. Moreover, the knowledge that delayed treatment will probably also be effective should prompt the physician to withhold treatment in questionable cases until the culture report is obtained on the following day.

Although treatment of the acute streptococcal infection is the best method available at present for the prevention of initial attacks of rheumatic fever in the general population, this method is not the best for preventing recurrent attacks in known rheumatic subjects. Because of the number of asymptomatic or atypical infections, reliance should not be placed on this approach. Such individuals should receive some form of continuous prophylaxis.

Although present evidence indicates that streptococcal infections should be routinely treated with penicillin, some question remains concerning the necessity of treating streptococcal infections in infants, since rheumatic fever is rare in this age group. Furthermore, the physician should be aware of the risks and disadvantages of penicillin treatment. In addition to the occasional reactions encountered, such treatment suppresses the production of type-specific antibodies which protect the individual from reinfection with this type.[103,104] The long-term effects of repeated suppression of protective antibody formation are not known. Since it is reasonable to assume that the decreased incidence of streptococcal infection in adult life compared to childhood is in part the result of the development of antibodies to a number of types, the inhibition of this immune response may ultimately result in an adult population which is as susceptible to streptococcal infection as present day school children.[37]

In summary, the management of acute streptococcal infection should be directed toward the prevention of suppurative and nonsuppurative complications and toward the prevention of transmission of infection to other people, since little can be done to alter the acute course of the disease. Penicillin seems to be the best drug for this purpose. Sulfadiazine should not be used, and the tetracyclines should only be employed in patients sensitive to penicillin. Limited evidence indicates that Erythromycin is equally as effective as penicillin, but it seems logical to reserve this more expensive drug for the treatment of infections due to other bacteria, such as staphylococci, which may be resistant to penicillin. Eradication of the infecting organism appears to be essential, and this can be achieved with most assurance when treatment is continued for ten days. Intramuscular preparations which appear to be effective include crystalline procaine penicillin G in oil with aluminum monostearate, crystalline procaine penicillin G, and DBED penicillin (dibenzylethylenediamine dipenicillin G). The first two have the disadvantage that multiple injections are required, whereas the last drug gives more local and, in adults, more systemic reactions. The treatment of streptococcal infections with oral penicillin reduces the incidence of acute rheumatic fever, but the dosage has not been well established. Even treatment begun after the patient is asymptomatic significantly reduces the incidence of acute rheumatic fever. Although routine treatment of streptococcal infection is recommended to prevent initial attacks of rheumatic fever, this approach should not be relied upon in known rheumatic subjects. Furthermore, some disadvantages, such as the inhibition of the development of protective antibodies, should be recognized as an expected result of treatment.

THE PREVENTION OF INFECTION

The development of a rational approach to the over-all problem of prevention of respiratory infections, including those caused by group A streptococci, has been hampered by a lack of definitive knowledge of the manner by which these diseases are transmitted. Group A streptococci can be found in both the upper respiratory tract and the environment, but little information has been available concerning the relative importance of these two reservoirs of infection. It has not been demonstrated whether the majority of spread occurs by direct contact with individuals harboring streptococci or by indirect means, such as contact with contaminated air, dust, clothing, or bedclothing. Most recent interest in this problem has centered around means of measuring, understanding, and controlling environmental contamination, particularly contamination of air and dust. Although methods have been devised which markedly reduce the number of group A streptococci in the environment, no consistent or satisfying effect on the incidence of streptococcal infections has been demonstrated.[22] This failure is apparently because air-borne and dust-borne routes are relatively unimportant in the transmission of streptococcal infections. Studies at the Streptococcal Disease Laboratory[20] indicate that, although group A streptococci can often be cultured from blankets or dust in large numbers, exposure to such contaminated blankets or inoculation with such dust does not ordinarily result in infection. Furthermore, the geographic pattern of spread within a group fits more with spread by direct contact than with spread by air-borne routes.[22] These studies suggest the importance of human reservoirs in the spread of streptococcal infections. They also confirm the reports of others[85] that certain kinds of carriers, for example, nasal carriers, are particularly apt to disseminate infection. Thus, present knowledge indicates a need for redirection of efforts to control spread along different lines. Mention has already been made of the importance of eradicating streptococci from the upper respiratory tract of patients with streptococcal infection to prevent further spread. Obviously this should also apply to known carriers. Methods of controlling spread by limiting direct contact between men have not been well studied, but it appears that avoidance of crowding or use of partitions might be effective.

Since there is some evidence that streptococcal infections occur less frequently in warmer climates, some consideration has been given to the avoidance of infection by moving to such climates.[11] However, this is not a practical solution to the problem, and probably no areas are completely free from streptococcal disease.

Tonsillectomy has been recommended both as a routine prophylactic measure in normal children and as a special procedure in rheumatic patients. Published reports concerning the effects of tonsillectomy are somewhat controversial as many lack adequate bacteriologic data or control groups. Therefore, the conclusion must be made that there is little evidence to indicate that removal of tonsils reduces the incidence of streptococcal disease or rheumatic fever.[20,105] The decline in infections which is frequently reported after removal of tonsils is a natural decrease which occurs with age in all children. Tonsillectomy does appear to reduce the number of suppurative complications[20] and thereby reduces the number of infections which are brought to the physician's attention. If such is the case, it seems an injustice to remove an organ which may make a difference as to whether streptococcal infections are recognized and treated. Furthermore, removal of tonsils does not seem warranted merely to prevent suppurative complications, since, with available antibiotics, these complications are readily prevented or cured.

Attempts to prevent streptococcal infection by immunization have not been successful.[105] Immunization against scarlet fever (erythrogenic) toxin, although possible, is of little value. Such immunization may protect against the development of a skin rash but it will not protect against infection. Crude vaccines prepared from heat or ultraviolet killed suspensions of streptococci have been tried, but uniform protection could not be demonstrated and reactions were frequent and severe.[106,107] Present methods for obtaining purified preparations of streptococcal components are limited, and no attempts have been made to immunize with such fractions as M protein. Since immunity to streptococcal infections is type-specific,[22] it appears that an effective vaccine would have to be polyvalent.

The sulfonamides and antibiotics have proved to be our most useful tools in the prevention of group A streptococcal infections. The use of these drugs appears to be indicated in two circumstances: (1) in population groups where streptococcal disease has become or is threatening to become epidemic, and (2) in rheumatic subjects.

Sulfadiazine was used extensively during World War II to control epidemics of streptococcal infection in military populations.[108] The drug was initially effective, but the emergence of resistant strains of streptococci curtailed its effectiveness. In addition, a few fatal reactions

were reported. Most recent studies have concerned the use of penicillin in such populations. Penicillin has several advantages over sulfadiazine. Penicillin resistance has never been observed among freshly isolated strains of group A streptococci.[91] With penicillin, group A streptococci can be eradicated from the oropharynx, whereas sulfonamides merely suppress streptococcal growth.[86,92] Serious drug reactions may be less with penicillin than with the sulfonamides.[88]

In order to eradicate streptococci from the throats of carriers, a minimum oral dose of 500,000 units twice daily for ten days seems necessary.[88] A single injection of 600,000 units of DBED penicillin may accomplish the same result.[88] Mass prophylaxis with oral penicillin in a dosage of 250,000 units twice daily for ten days[89,90] suppresses hospital admissions for streptococcal disease. Daily oral doses of 50,000 or 125,000 units have also been reported to show some effect.[89,91] Toxic reactions to oral penicillin are consistently recorded as less than 1 per cent.[88–91]

The prevention of streptococcal infections in individuals who have had rheumatic fever or chorea is of utmost importance, since the risk of rheumatic recurrence following streptococcal infections is so great in these individuals. A number of reports have appeared attesting to the efficacy of sulfonamide prophylaxis in these patients. These have been reviewed by Wilson[109] and more recently by Denny.[105] If the data from these reports are combined, an 85 per cent reduction in the expected number of recurrences is obtained. Sulfadiazine appears to be used most often although others, including sulfisoxazole,[110] have been used. The recommended dosage for sulfadiazine is 0.5 gm. a day for children under 60 lb. and 1 gm. a day for all other patients.[111] Since World War II, the prevalence of strains of group A streptococci resistant to sulfonamides has not been a problem in either military or civilian populations. It should be re-emphasized that whereas sulfonamides are ordinarily perfectly adequate for continuous prophylaxis, they are inadequate for the treatment of acute streptococcal infections.

Penicillin has been extensively employed for prophylaxis in rheumatic subjects in recent years. Most studies have employed oral preparations. Buffered tablets of sodium or procaine penicillin G have ordinarily been used, but oral DBED penicillin in tablet or liquid form has also been employed.[112] The minimum dose has not been well established. Some investigators have used as little as 100,000 or 200,000 units daily,[113,114] but this dosage does not appear to be sufficient since recurrences have occurred in patients on such doses.[115] The dose currently recommended by the Committee on Prevention of Rheumatic Fever of the American Heart Association[111] is 200,000 to 250,000 units twice daily. The penicillin should be taken on an empty stomach. Preliminary reports on the use of monthly intramuscular injections of DBED penicillin in a dosage of approximately 1,250,000 units as prophylaxis in rheumatic subjects are encouraging,[100,101,116] but since not all patients maintain a detectable level of penicillin for four weeks, this regimen may not give maximum protection in every patient. The choice between oral and long-acting repository penicillin may ultimately have to be made on an individual basis, since some patients cannot be relied upon to take oral medication, whereas others may dislike the painful injections incurred with DBED penicillin. Toxic reactions are uncommon with oral penicillin. Although few systemic reactions have been reported with the use of periodic intramuscular injections of DBED penicillin in rheumatic subjects, experience to date has been less extensive than with oral preparations and has been largely limited to children. Evidence that reactions may occur not infrequently in normal adults[20,102] suggests need for carefully controlled studies in normal children, since manifestations of serum sickness may be confused with rheumatic symptoms in rheumatic subjects.

Before sulfadiazine or penicillin is started in prophylactic doses, it is recommended that the rheumatic patients first be given a ten-day course of penicillin in therapeutic doses. This procedure is to eradicate group A streptococci from the throat, thereby avoiding confusion if a similar organism is isolated at some later date.

Regardless of which drug is used, year-round prophylaxis seems advisable since streptococcal infections may occur in the summer months.[111] The length of time prophylaxis should be continued must be determined on an individual basis. It depends in part on the risk of acquiring another streptococcal infection and on the risk involved if a rheumatic recurrence develops. Obviously, the risk of acquiring a streptococcal infection varies with age so that the Committee on Prevention of Rheumatic Fever of the American Heart Association[111] has recommended that prophylaxis be continued in children until at least 18 years of age. Regardless of age, however, it appears wise to continue prophylaxis if the risk of acquiring a streptococcal infection is great, such as may occur when a young adult enters the service. In general, the committee

recommends that prophylaxis be continued in adults for at least five years after the last attack. Here again, if recurrences are apt to be serious, as they may be in those with severe heart damage, prophylaxis continued for longer periods of time, perhaps for life, seems advisable.

In summary, the prevention of infection by controlling spread has been hampered by a lack of knowledge as to how streptococcal infections are transmitted. Spread by direct contact with individuals harboring streptococci seems to be more important than spread by air-borne routes although no good methods, except possibly avoidance of crowding, are available for limiting such contact. Tonsillectomy does not prevent the acquisition of streptococcal infections, and immunization attempts have so far not been successful. In recent years, the sulfonamides and penicillin have been useful in preventing streptococcal infections in epidemic situations and in rheumatic subjects. Penicillin, although more expensive, is regarded as having some slight advantage over the sulfonamides, since no group A strains have been encountered which are naturally resistant to this antibiotic. Furthermore, the organism can be eradicated with penicillin, and reactions are perhaps less common. All patients who have had acute rheumatic fever or chorea should be given a ten-day course of penicillin in therapeutic doses and then placed on year-round prophylaxis until 18 years of age or, in adults, for at least five years after the attack. Recommended dosage for continuous sulfadiazine prophylaxis is 0.5 to 1 gm. a day and for penicillin, 200,000 to 250,000 units once or twice daily. Limited but encouraging information is available on the use of monthly injections of DBED penicillin as prophylaxis in rheumatic subjects. In children, reactions appear to be infrequent regardless of which drug or preparation is used, although experience has been less extensive with DBED penicillin.

CONCLUSIONS

There no longer seems to be any reasonable doubt concerning the importance of group A streptococcal infections in the etiology of acute rheumatic fever and acute glomerulonephritis. In spite of this undeniable relationship, the pathogenesis of these diseases is still not clear. Variation in host response is well recognized but poorly understood. Recent studies have attracted attention to the significance of strain variation in the etiology of acute glomerulonephritis and to the importance of the persistence of the infecting streptococcus in the pathogenesis of acute rheumatic fever.

At the present time, the control of acute rheumatic fever and acute glomerulonephritis can best be accomplished through the control of acute streptococcal infections. Adequate treatment of acute streptococcal infections with penicillin prevents acute rheumatic fever and probably reduces the incidence of acute glomerulonephritis. For therapy to be adequate, the organism must be eradicated; this seems to depend primarily on the length of time treatment is continued. Continuous prophylaxis with either sulfadiazine or penicillin prevents rheumatic recurrences by preventing streptococcal infection. Prophylaxis should be continued as long as risk of infection or further cardiac damage is great.

Complete control of streptococcal infections and their sequelae cannot be expected through the use of antimicrobial agents. The difficulties of differential diagnosis of upper respiratory infections and the frequency of subclinical and atypical streptococcal infections make this impossible. In addition, the long-term effects of the repeated use of these agents is not known. Further advances in the prevention of these diseases will depend on additional knowledge of their pathogenesis and continued inquiry into modes of spread and immunization methods.

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Aureomycin is the trade name for chlortetracycline and is a product of Lederle Laboratories.

Terramycin is the trade name for oxytetracycline and is a product of Pfizer Laboratories.

N, N' dibenzylethylenediamine dipenicillin G is variously designated in the literature as DBED penicillin, benzethacil, and benzathine penicillin G. First introduced by Wyeth Laboratories under the trade name Bicillin.

Gantrisin is the trade name for sulfisoxazole and is a product of Hoffmann-La Roche.

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Recognition of Abnormal Hemoglobin Syndromes

ROBERT H. ALWAY, M.D.
Denver, Colorado

Since Pauling, Itano, Singer, and Wells reported the first abnormal hemoglobin in 1949,[1] three additional abnormal hemoglobin species have been identified.[2-4] It now appears likely that many of the variants of the thalassemic and sickle-cell syndromes may result from various combinations of these abnormal hemoglobins with normal hemoglobin. The too simple division into Cooley's anemia occurring in people of Mediterranean origin and sickle-cell disease in Negroes must be abandoned to consider more than a dozen variations in racial groups other than Negroes and Mediterranean peoples.

Thalassemia, although not primarily a hemolytic disorder, has enough in common with sickle-cell disease to be considered with it. The thalassemic syndrome should be included in any discussion of abnormal hemoglobin syndromes even though it appears to result from an inherited abnormality in hemoglobin metabolism rather than from the presence of an abnormal adult hemoglobin.

NORMAL HEMOGLOBIN

There are 2 normal hemoglobins, fetal (F) and adult (A). Normal and abnormal hemoglobins are labelled according to the accepted terminology.[5] Hemoglobin F is produced in the human fetus, constituting from 55 to 98 per cent of the total hemoglobin at birth.[6-8] Normal hemoglobin A appears early in the fetus, 6 per cent having been demonstrated in a 20-week fetus.[9] Hemoglobin F in amounts less than 5 per cent cannot be demonstrated by electrophoresis, but, with Singer and Chernoff's modification of hemoglobin alkaline denaturation, as little as 2 per cent fetal hemoglobin can be determined.[6]

After 5 years of age, hemoglobin F is not normally demonstrable by alkaline denaturation. By other methods, however, amounts less than 2 per cent of hemoglobin F can be demonstrated in an occasional normal adult blood.[10] Smith and Conley have recently accomplished satisfactory separation of hemoglobin F from hemoglobin A by filter-paper electrophoresis.[11] Hemoglobin F normally is present in only small amounts after age 30 months. In certain chronic anemias, however, the production of hemoglobin F may continue indefinitely.[12] The ready demonstration of more than 2 per cent hemoglobin F beyond infancy suggests interference with hemoglobin A synthesis or a continued hemolytic process such as thalassemia, sickle-cell anemia, or related diseases. Other hereditary hemolytic disorders and severe blood dyscrasias usually show hemoglobin A.

The alkaline-resistant component present in the various sickling syndromes has been found to be identical with normal fetal hemoglobin electrophoretically, spectrophotometrically, and immunologically.[7, 13, 14]

Table 1 summarizes differences between fetal and adult hemoglobins. These data have facilitated the demonstration that hemoglobin F seen in the newborn and the alkaline-denaturation-resistant fraction noted in the abnormal hemoglobin syndromes are probably identical.

ABNORMAL HEMOGLOBINS

The 4 abnormal hemoglobins, S, C, D, and E, may be recognized in individuals in a variety of combinations with hemoglobins A and F. Table 2 shows the hemoglobin species present in individuals with pertinent inherited and acquired conditions. The means of identifying the abnormal hemoglobins and the trait or heterozygous states of each may be conveniently considered at this point. Clinical and laboratory differentiation of the abnormal hemoglobin syndromes will be discussed subsequently.

Hemoglobin electrophoresis

The demonstration by Pauling and his associates of a hemoglobin with abnormal electrophoretic mobility in sickle-cell anemia and the subsequent reporting of additional abnormal hemoglobins made necessary a relatively simple and inexpensive means of determining the electrophoretic mobilities of hemoglobins. Several investigators have reported the satisfactory application of filter-paper electrophoresis to this problem.[11, 15, 16] A solution of the hemoglobin mixture in question is put on filter paper, which is placed in a buffer.

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TABLE 1

SUMMARY OF DIFFERENCES BETWEEN FETAL AND ADULT HEMOGLOBINS*

Phenomenon	*Distinctive properties*
Alkaline denaturation	Fetal hemoglobin is more resistant than adult.
O_2 dissociation curve	Fetal hemoglobin inside the erythrocyte has higher oxygen affinity and smaller value of 'n' in the Hill equation than adult hemoglobin.
Solubility behavior	Definite difference is seen in the solubility curves between human adult and fetal hemoglobin CO, hemoglobin O_2, and methemoglobin; in strong phosphate buffer, fetal hemoglobin is more than 6 times as soluble as adult hemoglobin.
Crystallographic data	Different characteristics are seen in crystalline forms.
Spectroscopic differences	In human fetal hemoglobin, the fine tryptophan absorption band appears at 289_{μ}; in adult hemoglobin, at $291O_{\mu}$. The band is maximum in its absorption spectrum at 2898 A.[20]
Amino acid composition	Human fetal hemoglobin contains 2.6 terminal valyl residues per molecule compared with 5 in human adult hemoglobin; bovine adult hemoglobin contains more histidine than fetal hemoglobin.
Peroxidative effect	Human fetal hemoglobin exhibits greater peroxidative activity than adult hemoglobin.
Electrophoretic mobility	In 0.01 mg. of sodium phosphate, adult hemoglobin has a higher mobility than fetal hemo-globin.[9] It also can be qualitatively separated by paper electrophoresis.[11]
Antigenic specificity	Relatively large differences are seen in specificity.[10, 13]

*Modified from Gardikas et al.[61]

An electric field is then imposed. The extent or rapidity of movement of the hemoglobin molecules serves to delineate the species present, which is then revealed by a dye. With this method, the presence of electrophoretically normal and abnormal hemoglobins can be determined on several as well as on individual specimens to permit simultaneous comparison with the patient's parents and siblings.

An approximation of the amounts of hemoglobins A, S, and C may be obtained from filter-paper electrophoresis.[11, 15] Standard electrophoretic equipment, however, permits more accurate definition and quantitation. These hemoglobins may be demonstrated readily in hemoglobin solutions by their different electrophoretic mobilities. Filter-paper electrophoresis of the mixture A-C-S would separate as C-S-A, with A farthest from the baseline.

Hemoglobin D has the same migration pattern as hemoglobin S.[3] Therefore, the rare double heterozygote, S-D, cannot be recognized by electrophoresis.

The fourth abnormal hemoglobin has been designated type E.[4] By both filter-paper and standard electrophoresis at an alkaline *p*H, hemoglobin E's mobility is less than hemoglobin S's and greater than hemoglobin C's. At a lower *p*H, however, the electrophoretic mobility of hemoglobin E is less than that of hemoglobin C.

TABLE 2

ABNORMAL HEMOGLOBIN SYNDROMES*

Condition	*Hemoglobin species present*					
	A	F	S	C	D	E
Normal adult	+	±	—	—	—	—
Normal newborn	+	+	—	—	—	—
Simple hypochromic microcytic anemia	+	—	—	—	—	—
Some acquired anemias	+	+	—	—	—	—
Sickle trait	+	—	+	—	—	—
Sickle-cell anemia	—	+	+	—	—	—
Sickle-cell thalassemia	+	+	+	—	—	—
Sickle-cell hemoglobin C	—	±	+	+	—	—
Sickle-cell hemoglobin D	—	+	+	—	+	—
Hemoglobin C trait	+	—	—	+	—	—
Homozygous hemoglobin C	—	—	—	+	—	—
Thalassemia hemoglobin C	?	+?	—	+	—	—
Thalassemia minor	+	±	—	—	—	—
Thalassemia major	+	+	—	—	—	—
Hemoglobin D trait	+	—	—	—	+	—
Hemoglobin E disease	—	+	—	—	—	+

*Modified from Itano.[7]

Genetics

The several abnormal hemoglobins seem to be genetically determined. It was first suggested that sickle-cell disease and thalassemia resulted from inheritance of a dominant gene.[17] Neel[18] and Beet[19] offered the hypothesis that the heterozygous state as regards sickling (S-A) is represented as a sickle trait, whereas homozygosity (S-S) results in sickle-cell anemia. It would appear that a similar explanation holds for thalassemia minor and thalassemia major.[20] The demonstration of hemoglobin S in nonsicklers further supports Neel's hypothesis.[21] It now seems safe to suggest that, when a patient with sickling and a hemolytic process has only 1 parent positive for sickling, further examination of the nonsickling parent's blood may reveal either less than 7 per cent of hemoglobin S or hemoglobin C, D, or E or evidence of the thalassemia trait.[3]

Abnormal hemoglobin traits

Persons heterozygous for the sickling gene (S-A) are referred to as showing the sickle-cell trait. The heterozygous form of abnormal hemoglobins C, D, and E may be referred to similarly. The term for the condition with thalassemia gene heterozygosity, however, is thalassemia minor.

Sickling. Erythrocytes containing 7 to 10 per cent or more of hemoglobin S will sickle when in an environment with reduced oxygen tension.[22, 23] Hemoglobin specimens of sickle-cell anemia show very low solubility as amorphous ferrohemoglobin, as compared with sickle-cell trait and sickle-cell hemoglobin C or D disease.[24] Of hemoglobins A, F, and S, only the latter forms tactoids.[12] The sickling occurring in sickle-cell anemia, homozygous form (S-S), is chiefly filamentous. The same may hold in other forms of sickle-cell disease if the proportion of hemoglobin S is high. In sickle-cell anemia, sickling may be seen on peripheral smears. In the other sickle-cell syndromes, however, sickling must be shown in vitro under conditions that produce reduced oxygen tension. In sickle-cell trait, sickling develops more slowly and with a predominance of holly-leaf rather than filamentous forms. Sickling in thalassemia sickle-cell disease and in sickle-cell hemoglobin C disease is more rapid and similar to that in sickle-cell anemia.

It should be stressed that a negative sickling test does not preclude the presence of hemoglobin S in a concentration of less than 7 per cent.[25] Another pitfall in evaluating sickling may be the failure to demonstrate it initially. Banks et al. reported that, in the first preparation, the erythrocytes of 20 per cent of the parents of children with sickle-cell anemia failed to sickle. Only 4 per cent were negative on a second attempt.[26]

Sickling technics. Reducing agents such as freshly prepared 2 per cent sodium metabisulfite solution,[27] *Bacillus subtilis* culture,[28] sodium dithionite,[29] or hydrogen sulfide or BAL[30] give more rapid and consistent results than does the technic of sealing a drop of blood under a coverslip and observing for sickling twenty-four and forty-eight hours later. The commonly employed method of combining preliminary five-minute venous stasis with a forty-eight-hour sealed preparation[31] is not as satisfactory as the use of reducing agents.

Incidence of sickling. Sickling may be demonstrated in about 10 per cent of American Negroes with sickle-cell anemia occurring in about 1 in 40 of these. Widely divergent reports have appeared on the incidence of sickling among African Negroes. The highest reported incidence, about 20 per cent, is found across the middle of Africa. No adequate explanation has been offered for the small number of sickle-cell anemia cases reported.

It should be remembered that sickling is not limited to Negroes or to those races with a likely admixture of Negro traits.[32] A very high incidence of sickling was reported in Greece by Caminopetros.[33] This subsequently was disputed by Choremis et al.,[34] who pointed out the apparent misinterpretation of bizarre-shaped cells which were not actually sickled. The false sickling was fusiform rather than holly leaf, filamentous, or crescentic. It was noted that repeated specimens from the same individual did not give consistent results. When a similar population was sampled, using reducing agents rather than the less dependable occlusive coverslip method, sickling could not be demonstrated.[34]

Sickle-cell trait. The erythrocytes of individuals heterozygous for the sickling factor sickle more slowly and show more holly-leaf than filamentous forms. Hemoglobin electrophoresis shows 24 to 45 per cent hemoglobin S and 55 to 76 per cent hemoglobin A.

Sickling in a Negro child with anemia due to iron deficiency may be confusing, as may be other causes not associated with abnormal hemoglobins. In all individuals whose blood sickles, the parents and siblings should be checked for sickling. This should be done even when sickling is slow and atypical for sickle-cell anemia.

Hemoglobin C trait. This condition is asymptomatic, with no physical findings or consistent hematologic changes beyond leptocytosis. Kaplan et al. report frequent increase in target cells up to 33 per cent.[35] Others have noted this less consistently.[11, 36] In one series, 4 of 7 showed decreased osmotic fragility of erythrocytes.[35] The unique finding of a short erythrocyte survival time first reported was not borne out in further cases of hemoglobin C trait studied by Kaplan et al.[35, 37]

The presence of hemoglobin C may be suspected when an increased number of target cells is noted in the peripheral blood smear. Its presence, however, can be shown only by electrophoresis.[36]

Target cells may be seen in association with dehydration, after splenectomy, and with liver disease[38] and steatorrhea as well as in the Mediterranean hemopathies, sickle-cell disease, iron-deficiency anemia, and various combinations of hemoglobin C. Obviously, leptocytosis is not specific. Occasionally, 2 to 3 per cent of target cells is seen in Caucasians and up to 5 per cent in healthy Negroes. Usually, however, less than 1 per cent will be noted in a normal peripheral

smear.[37] Target cells are seen with greatest frequency in sickle-cell hemoglobin C disease, homozygous hemoglobin C individuals, sickle-cell anemia, and hemoglobin C trait.[37]

Hemoglobin D trait. As previously noted, hemoglobin D has the same electrophoretic mobility as hemoglobin S, but does not produce erythrocyte sickling. Solubility studies, which show a low solubility for hemoglobin S compared to hemoglobin D, are necessary for differentiation of the latter.[3, 24]

Hemoglobin E trait. This has not as yet been reported.

Thalassemia minor. This represents the heterozygous form of the thalassemia gene. Rich suggests that the thalassemia allelomorph interferes with the synthesis of normal adult hemoglobin.[39] Thalassemia minor is characterized by microcytosis, anisopoikilocytosis, ovalocytosis, or leptocytosis and decreased erythrocyte osmotic fragility. There may be moderate hypochromia and polycythemia. The familial incidence and failure to respond to antianemia therapy further differentiate this condition from iron-deficiency anemia. Wintrobe states that this condition may vary from a mere red cell abnormality to an obvious clinical disorder with moderate hypochromic, microcytic anemia, icterus, and splenomegaly.[32]

By the usual methods, electrophoretic analysis of hemoglobin solutions from individuals with thalassemia minor reveals only a component of normal mobility. An appreciable amount of alkaline-resistant hemoglobin may be found.[40]

SICKLE-CELL SYNDROMES

Sickle-cell disease is generally the homozygous form (S-S), but, in occasional families in which only 1 parent shows sickling, the other parent will be heterozygous for 1 of 3 other genes associated with a hematologic disorder: hemoglobin C or D or thalassemia. Confusion has arisen because of the indiscriminate use of the terms sickle-cell disease and sickle-cell anemia. In the following discussion, sickle-cell disease will include the 4 genetically, physicochemically, and immunologically distinguishable types showing sickling and a chronic hemolytic disorder of varying degrees of severity. The forms of sickle-cell disease now recognized are: (1) sickle-cell anemia, (2) sickle-cell thalassemic disease, (3) sickle-cell hemoglobin C disease, and (4) sickle-cell hemoglobin D disease. Sickle-cell anemia refers specifically to the homozygous condition (S-S). Table 2 shows the hemoglobin species in the 4 forms of sickle-cell disease as well as the sickle-cell trait. Sickle-cell disease was first described in 1910 by Herrick, who noted peculiar sickle-shaped erythrocytes in a Negro student with severe anemia.[41]

1. *Sickle-cell anemia.* This is a chronic illness marked by crises of pain and exaggeration of the hemolytic process. Pain may be musculoskeletal or in the head, chest, or abdomen. Sickle crises are not infrequently confused with rheumatic fever or acute surgical abdominal conditions. Central nervous system manifestations, including coma, convulsions, and paralysis, may add to the confusion.

This persistent hemolytic anemia occurs in Negroes who are homozygous for the sickling trait. Both parents are carriers of the trait. Manifestations are rare in the first six months of life and more frequently first appear during the second year. Splenomegaly may be manifest early, but the spleen characteristically is not palpable in later childhood or in adulthood. Chronic cutaneous ulcers over the internal and external malleoli may develop on the legs of adolescents and adults. The sedimentation rate is slow even when anemia is severe.[42] The peripheral smear shows leptocytosis, nucleated red cells, and polychromatophilia. The sickling is filamentous. Erythrocytes show increased resistance to hypotonic saline, and their survival time when transfused into a healthy doner is shorter than normal. Electrophoresis shows the presence of 76 to 100 per cent hemoglobin S.[1, 43] The remainder of the hemoglobin is usually type F.

2. *Sickle-cell thalassemic disease.* This is the third in frequency of the sickle-cell syndromes. It is generally more severe than sickle-cell hemoglobin C disease, but prognosis is better than with sickle-cell anemia. This syndrome, also referred to as microdrepanocytic anemia, probably accounts for most of the sickle-cell disease in non-Negroes.[40] Banks et al., however, reported 1 case occurring in a Negro boy.[26]

Sickle-cell thalassemic disease was first reported in the United States in 1950.[44] Reports had appeared in Italian literature, however, since 1946.[45] The first example reported in this country was diagnosed as sickle-cell anemia. A 38-year-old male, rheumatic since childhood with episodes of fever and jaundice, showed 100 per cent sickling. His spleen was slightly enlarged. In this country, subsequent reports of the syndrome have varied from severe chronic hemolytic anemia to thalassemia minor.[26, 40, 46-48] In all reports, the persistence of or the finding of an enlarged spleen beyond childhood has been noteworthy. The blood picture is generally consistent with a diagnosis of sickle-cell anemia. One parent of the affected patients has been shown to be

heterozygous for thalassemia and the other for the sickling trait.

Electrophoretic and other studies of the hemoglobin mixtures have shown the presence of hemoglobins S and F. Itano showed that the slow component had the same electrophoretic mobility as hemoglobin F.[14] This has been shown to be immunologically similar to F. Itano has subsequently demonstrated the presence of hemoglobins S, F, and A in sickle-cell thalassemic disease. The apparent percentage of hemoglobin S varies between 61 and 84 per cent, being less than the 76 to 100 per cent in sickle-cell anemia.

3. *Sickle-cell hemoglobin C disease.* This, the second most common type of sickle-cell disease, was first described by Kaplan et al.[35] Subsequently, they and others have expanded the clinical, hematologic, and genetic aspects.[11, 36, 37]

Sickle-cell hemoglobin C disease is characterized by a mild hemolytic syndrome, rapid and filamentous sickling, and splenomegaly persisting in adult life. Crises are not the rule but may occur in infancy or early childhood as well as in pregnant adult females.[11, 36] This syndrome is less severe than sickle-cell anemia or sickle-cell thalassemic disease. The hematologic findings are consistent with mild sickle-cell anemia, with the notable exception that target cells are generally very prominent.

Leptocytosis may be noted in sickle-cell anemia, sickle-cell trait, sickle-cell hemoglobin C disease, hemoglobin C trait, and thalassemia major and minor. Ranney et al.[36] and Smith and Conley,[11] reporting sickle-cell hemoglobin C disease in somewhat older patients than those seen by Kaplan et al., mention 4 patients with gross hematuria. In both of these series, more severe crises as well as episodes of musculoskeletal pain were notable.

Hemoglobins S, C, and F—the latter inconsistently—may be present in sickle-cell hemoglobin C disease, which has been so far described only in Negroes. The percentages of each hemoglobin in this syndrome are: hemoglobin S, 33 to 48 per cent; C, 50 to 67 per cent; and F, 2 to 3 per cent.

4. *Sickle-cell hemoglobin D disease.* This infrequent sickle-cell disease is apparently the result of the combination of the gene for hemoglobin S and that for a third abnormal hemoglobin, type D. Recognized in but 2 apparent Caucasians, it has been only briefly reported.[3] Two anemic, sickle-cell hemoglobin D individuals with 4 normal siblings were found. Their parents' hemoglobin solution showed an electrophoretic pattern similar to the sickle-cell trait (S-A), but the erythrocytes of only 1 could be made to sickle. Further investigation showed a hemoglobin with greater solubility than hemoglobin S. Subsequently, Itano showed that the hemoglobin mixture in these 2 anemic individuals consisted of types S, D, and F, while the hemoglobin D showed types A and D.[14]

Summary. The 4 sickle-cell diseases, presented in order of decreasing severity, can be summarized in the following comments. *Splenomegaly* in sickle-cell anemia tends to disappear before adolescence, while it tends to be persistent and may be progressive in the second and third forms. *Sickling* may be demonstrated in all 4 types but is most evident in sickle-cell anemia, in which it may be seen in peripheral smears. *Target cells* are usually seen most frequently in sickle-cell hemoglobin C disease and then in sickle-cell anemia and microdrepanocytic anemia. *Race* may be helpful in that Negroes account for almost all sickle-cell anemias and sickle-cell hemoglobin C disease, while, with a single exception, sickle-cell thalassemia and sickle-cell hemoglobin D disease have been reported in Caucasians.

For definite diagnosis, however, the hemoglobin types in patient, parents, and siblings should be ascertained.

HOMOZYGOUS HEMOGLOBIN C DISEASE

The 5 cases reported[36, 49-52] show a similar pattern: a moderate compensated hemolytic process, leptocytosis, minimal to moderate splenomegaly, and decreased osmotic fragility of erythrocytes. In 2 instances, the patients' erythrocytes, when transfused into a normal donor, have shown decreased survival times. Cholelithiasis[50, 52] and arthralgia[36, 52] have been reported, as well as chronic jaundice and abdominal pain.[49] The absence of sickling or of marked hypochromasia and microcytosis helps differentiate homozygous hemoglobin C disease from the various forms of sickle-cell disease and thalassemia. It is noteworthy that 1 case occurred in a Sicilian,[49] the others being Negroes. Absolute diagnosis depends on the demonstration by electrophoresis of the presence of only hemoglobin C.

The double abnormal heterozygote C-D has not been reported. Kaplan et all.[37] mention that they have recognized and will report a case of hemoglobin C thalassemic disease.

HEMOGLOBIN E DISEASE

A fourth type of abnormal hemoglobin has been found by Itano.[4] The child's hemoglobin was found to be 45 per cent type F and 55 per cent the new type, hemoglobin E. At an alkaline *p*H, the mobility of hemoglobin E, both by filter-paper and moving boundary electrophoresis, is

greater than that of hemoglobin C but less than that of hemoglobin S. At *p*H 6.5, however, hemoglobin E mobility is slightly less than hemoglobin C. This latest abnormal hemoglobin resembles type A in its response to alkaline denaturation and in its ultraviolet absorption spectrum.

THALASSEMIC SYNDROME

Thalassemia minor disease, sickle-cell thalassemic disease, and hemoglobin C thalassemic disease have been considered in previous sections. Thalassemia, although not showing an abnormal adult hemoglobin, is characterized by abnormal production of hemoglobin F beyond the normal time of its virtual disappearance. Hemoglobin F may constitute 40 to 100 per cent of the hemoglobin mixture in thalassemia major.[20]

Cooley and Lee first clearly differentiated this anemia from von Jaksch's anemia in 1925.[53] The terms "Mediterranean disease" and "thalassemia" were introduced in 1936 by Whipple and Bradford, who suggested that an inborn error in hemoglobin metabolism might be an underlying factor.[54] In 1940 Wintrobe et al.[55] described an iron-resistant, hypochromic, microcytic anemia occurring beyond childhood. Apparently similar syndromes were described as target-cell anemia[56] and familial microcytic anemia.[57] In 1944, Valentine and Neel, discussing the genetics of this condition, suggested the terms "thalassemia major" for the severe anemia described by Cooley and Lee and "thalassemia minor" for the less severe anemia described by Wintrobe, Dameshek, Strauss, and others.[20] The heterozygous state is represented by thalassemia minor and the homozygous state by thalassemia major.

Thalassemia was at first thought to be limited to people of Italian, Greek, Syrian, or Armenian origin. Wintrobe, however, cites accepted cases occurring in Chinese, Indians, Egyptians, Spanish, Filipinos, Frenchmen, Mexicans, and Negroes.[42] A recent report stresses its high incidence among the Thai.[58]

Thalassemia major, the homozygous form, is associated with a severe decrease in production of hemoglobin A, resulting in a chronic fatal anemia of childhood, usually manifest in early infancy. Early and progressive splenomegaly is the rule. Erythrocyte changes are similar in character but more severe than those described in thalassemia minor. Hyperplasia of the bone marrow leads to a typical roentgenographic picture. Retarded development and mongoloid facies as well as maxillary overgrowth leading to malocclusion may be noted. An intracorpuscular defect is suggested by the fact that erythrocytes from patients with thalassemia major transfused into a normal recipient have decreased survival times.[59] Definite hypochromasia and microcytosis suggest the presence of the thalassemia gene in the abnormal hemoglobin syndromes.

SUMMARY

Clinical and laboratory findings of the blood dyscrasias considered above have so many common findings that it may help to present some useful common and differentiating points in tabular form (Table 3). Certain points in the preceding text as well as in Table 3 warrant reemphasis.

Filter-paper electrophoresis provides a relatively simple and inexpensive means of determining the electrophoretic mobilities of hemoglobins A, S, C, and F. Hemoglobins D and F may be recognized by further studies.

The presence of hemoglobin S is suggested by erythrocyte sickling. Although sickling is most conspicuous in ease and extent in sickle-cell anemia and sickle-cell thalassemic disease, it is also found in 3 other conditions. Leptocytosis suggests the presence of hemoglobin C. It is most marked in homozygous hemoglobin C disease

TABLE 3

DIFFERENTIAL POINTS IN ABNORMAL HEMOGLOBIN SYNDROMES

Condition	*Anemia*	*Sickling*	*Target cells*	*Hypochromic microcytosis*	*Splenomegaly*	*Arthralgia*
Sickle-cell trait	0	+	+	0	0	
Sickle-cell anemia	3+	3+	2+	0	+ to −	++
Sickle-cell thalassemia	2+	2+	+	+	++	++
Sickle-cell hemoglobin C	+	+	3+	+	++	±
Sickle-cell hemoglobin D	+	+	?	?	?	?
Hemoglobin C trait	0	0	2+	0	0	0
Homozygous hemoglobin C	±	0	2 to 4+	0	+	+
Thalassemia minor	±	0	+	2+	+	0
Thalassemia major	4+	0	+	4+	4+	0
Iron-deficiency anemia	+ to 4+	0	±	1 to 4+	±	0

but is also seen to a lesser extent in sickle-cell hemoglobin C disease, sickle-cell anemia, and hemoglobin C trait and in both thalassemia major and minor.

Erythrocyte hypochromia and microcytosis may be noted in the thalassemic conditions.

Splenomegaly is most marked in thalassemia major. It is progressive in sickle-cell thalassemic disease and sickle-cell hemoglobin C disease but regresses usually before adolescence in sickle-cell anemia. It is less marked in homozygous hemoglobin C disease and thalassemia minor.

It is of interest that arthralgia is noted not only in the 3 most common forms of sickle-cell disease but also may occur in individuals homozygous for hemoglobin C.

Hematuria is possibly of significance in sickle-cell hemoglobin C disease.

The siblings and parents of individuals suspected of the hemopathies discussed may be studied with often enlightening results. It should be reemphasized that it is no longer correct to consider thalassemic disorders to be peculiar to Italians, Sicilians, and Greeks or sickle-cell disease to be limited to Negroes.

Although definitive therapy is not available for these disorders, eugenic counselling and a more precise prognosis may now be offered to the afflicted families.

In the abnormal hemoglobin syndromes, the state of knowledge and its organization and usefulness are not unlike that for congenital cardiac defects in the relatively recent past. It is to be hoped that here, too, increasing knowledge and awareness will more quickly bring effective therapeutic measures.

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Advances in Diagnosis and Treatment of Epilepsy in Children

HADDOW M. KEITH, M.D.
Rochester, Minnesota

EPILEPSY, defined in its broadest sense, has afflicted man from earliest times. However, the history of epilepsy as a clinical entity begins with Hippocrates in about 400 B.C. His book, *On the Sacred Disease,* is the first known monograph on epilepsy. In its opening sentence, a distinct advance in understanding of the etiology of the disease is recorded, for, in Adams' translation from the Greek,[1] Hippocrates said: "It (epilepsy) appears to me to be nowise more divine nor more sacred than other diseases, but has a natural cause from which it originates like other affections." Hippocrates pointed out in considerable detail that the disease is divine only as all other diseases are divine and is curable no less than other disorders. Thus he took it out of the realm of fear and superstition and described it as a disease of the brain, suitable for study, explanation, and treatment.

There then followed a long period, about two thousand years, during which, as far as records show, no studies that advanced the understanding of the disorder were made. With the Renaissance, however, a broader and clearer conception of the various forms of epilepsy emerged. The physicians of the time made careful observations on the relation between head trauma, brain abscess, and recurring convulsions and on the relation of "fevers," syphilis, smallpox, and measles to convulsive disturbances.

The more recent study of epileptic convulsions begins with the work of Richard Bright[2] (1789-1858) of London and Bravais[3] of France in 1827. The former established a clear relationship between a local cortical lesion and the aura or onset of an attack. The latter studied "hemiplegic epilepsy," gave detailed descriptions of focal motor seizures, and considered the aura as virtually equivalent of local spasms of muscles. The careful clinical studies of Russell Reynolds[4] were published in 1861, but it was Hughlings Jackson[5] and William Gowers[6] of London, in the late nineteenth century, who opened the modern era of scientific investigations, understanding, and treatment. Jackson stated: "A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles." He considered that all varieties of epileptic convulsions, petit mal, grand mal, and focal seizures, could be considered primarily as forms of focal epilepsy and, therefore, that all were "symptomatic."

In the fifty years since Jackson's important contributions to the understanding of epilepsy, progress had been made in both diagnosis and treatment. In diagnosis, clinical observations and laboratory studies have had their share. The developments in clinical diagnosis have been in the use of roentgenography, as in roentgenograms of the skull and in pneumoencephalography, and in cerebral angiography.

The most extensive clinical and physiologic studies have been made by Penfield and Jasper[7] at the Montreal Neurological Institute. During the past twenty-five years, Penfield has made accurate observations of electric stimulation of the brains of patients under local anesthesia to study the sites of origin of epileptic attacks and to record observations in regard to functional localization. As a result, he has extended knowledge of the mechanisms of brain function and has developed to a considerable degree the surgical treatment, first attempted by Horsley, of certain patients with demonstrable and removable foci.

The laboratory has contributed an entirely new method of diagnosis, electroencephalography, which has already greatly advanced knowledge of mechanisms, localization, and results of treatment. Chemical laboratory studies also have been of value.

ROENTGENOGRAPHY

Roentgenograms of the skull frequently demonstrate no abnormalities in epileptic patients, and any abnormalities present usually are suggestive and not decisive. Calcification in various parts of the brain may indicate a lesion which, on further study, can be related to the convulsions. It must be recognized, however, that calcifica-

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

tion in the falx, choroid plexus, pineal body, and so forth may be "physiologic" and not indicate any etiologic lesion. In some cases, the undersurface of the skull becomes eroded due to defects in the dura, and this may indicate an epileptogenic lesion.

Pneumoencephalography, as described by Dandy,[8] has proved to be somewhat more helpful in diagnosis than has the plain roentgenogram. It can demonstrate gross abnormalities of one or more ventricles and connecting porencephalic cysts. It may confirm a diagnosis of asymmetry or displacement of the brain, thus indicating that unilateral or focal atrophy is present. In cases with focal signs and symptoms, it may show laking of air over the cortex in the area where laking would be expected, thus indicating a focus of abnormality. In cases in which increased intracranial pressure is suspected, ventriculograms may give similar evidence of lesions. Both these procedures are of chief value in the study of focal lesions and have mainly negative value if there is no obvious focus.

Injection of radiopaque substances into the cerebral arteries has been used in diagnosis of intracranial lesions since its demonstration by Moniz[9] in 1934. It is most useful in delineating aneurysms but, with further study, may be of value in diagnosis of other focal lesions.

ELECTROENCEPHALOGRAPHY

Berger,[10] in 1929, was the first to publish recordings of the electric activity of the human brain. Since that date, an enormous number of contributions to study of the brain have been made by this method, many of them in relation to convulsive disorders. An electroencephalogram is defined by Knott[11] as a "graph of change in voltage with reference to time, but the voltage changes being referable to the cerebral cortex." To this might be added, "to the subcortex or to the deep centers." Gibbs and Gibbs,[12] Jasper[13] and others have graphically described the various tracings recorded from normal persons of all ages and from persons with convulsive and other disorders.

Penfield and Jasper[7] stated: "Electrical signs of epileptic discharge consist principally of episodic, paroxysmal high voltage waves of varied forms and frequencies. Often, but not always, there are associated abnormal rates of cerebral discharge or dysrhythmia, tachyrhythmia or bradyrhythmia." In a study at the Montreal Neurological Institute, Penfield and Jasper found evidence of focal cortical epileptogenic lesions in more than half of all epileptic patients, if complete studies were made, including some type of activation such as that induced by pentylenetetrazol (Metrazol). These findings were gathered in a large clinic where every effort was made to determine the presence or absence of any surgical focus.

In the laboratory in Rochester, an analysis of electroencephalograms representing various clinical groups has been made by Bickford and White. Classification of the electroencephalographic results has been made according to the system of grading described. The clinical diagnoses were those made by the neurologists who examined the patients. The results are to be regarded as approximate only; due consideration should be given to the limitations of the classification of electroencephalograms that was used and to the inevitable minor differences in diagnostic terminology employed by different members of the staff. Before the analysis, diagnoses had been established with reasonable certainty.

Classification

1) Delta: Random slow waves (0.5 to 4 per second). Arrhythmic and nonrepetitive. Usually unaffected by eye opening and hyperventilation.

Grade I — Amplitude up to 30 microvolts
Grade II — Amplitude between 30 and 60 microvolts
Grade III — Amplitude above 60 microvolts

Also categorized as focal or generalized. For purposes of these statistics, bilateral deltas are classified as generalized.

2) Dysrhythmia: General category containing waves that are usually rhythmic and repetitive and that tend to be inhibited by eye opening and accentuated by hyperventilation. Also included in this category are specific wave forms.

Grade I — Minimal abnormalities, continuous or paroxysmal; amplitude up to 30 microvolts.
Grade II — Moderate abnormalities, continuous or paroxysmal; amplitude up to 60 microvolts.
Grade III — Specific wave forms, as, for example, spikes, sharp waves, spike waves, and so forth; also categorized as diffuse or focal

3) Asymmetry: An amplitude asymmetry of the alpha rhythm greater than 25 per cent.

4) Delta dysrhythmia: Mixtures of delta and dysrhythmia. To maintain simplicity, these have not been graded but are considered as a single, mixed group.

Grand mal (748 cases). These cases include all major seizures, alone or in combination with

other types of seizures, for which no etiologic agent could be demonstrated. The relatively high percentage of spike-wave records is partly accounted for by the occurrence of petit mal seizures in some of these patients. Results of special activation methods, such as use of Metrazol, are not included in the following statistics:

	Per cent		Per cent
Tracing normal	18	Focal dysrhythmia	2
Dysrhythmia, grade I	29	Focal delta	2
Dysrhythmia, grade II	25	Delta dysrhythmia	2
Dysrhythmia, grade III	22		

Petit mal (101 cases). In these cases, petit mal was unassociated with any other type of seizure.

	Per cent		Per cent
Tracing normal	16	Dysrhythmia, grade III	51
Dysrhythmia, grade I	14	Focal dysrhythmia	2
Dysrhythmia, grade II	15	Delta dysrhythmia	2

Psychomotor (75 cases). Cases characterized by mixed seizures and all cases proved or thought to be due to some other lesion of the temporal lobe, such as tumors, scars, and so on, are not included. Most of the dysrhythmias are generalized and bitemporal in distribution. In about 15 per cent of cases, there are focal discharges confined to the temporal lobe. Sleep and activation by Metrazol give useful information, although these data are not included in the statistics.

	Per cent		Per cent
Tracing normal	28	Focal dysrhythmia	6
Dysrhythmia, grade I	25	Nonfocal delta	2
Dysrhythmia, grade II	25	Delta dysrhythmia	6
Dysrhythmia, grade III	2	Focal delta	6

Normal controls (31 cases). The subjects were adults, aged 20 to 50 years, with no history of any disease known to affect the intracranial portions of the nervous system. Although the series is small, the findings are similar to those derived by other workers who studied larger groups. Usually, from 15 to 20 per cent of the supposedly normal population give abnormal records.

	Per cent
Tracings normal	85
Dysrhythmia, grade I	12
Dysrhythmia, grade II	3

Inclusion of records from the younger age groups would not appreciably alter percentages.

The foregoing statistics demonstrate that no single form of electroencephalogram is characteristic of any one clinical form of convulsive disturbance. The nearest approach to consistency is in the petit mal type of disturbance, wherein more than 50 per cent of the tracings exhibit the spike and wave of 3 per second activity.

It is important that electroencephalography be viewed as a valuable aid in diagnosis. However, its limitations should be understood. It cannot be used as a substitute for careful clinical appraisal. In many cases, moreover, it is unnecessary to establish a diagnosis. Many patients with convulsions are referred for an electroencephalogram, and parents have come to feel that this procedure will make the differential diagnosis for or against epilepsy and will indicate the form of treatment and the ultimate outcome. To a certain extent, this is true among physicians also, and they are disappointed when the findings do not solve all the diagnostic and therapeutic problems. This state of affairs no doubt is due in part to enthusiasm for a new scientific tool. There is no doubt, also, that more is gradually being learned about how to use this tool; it is reasonable to expect that, as knowledge and experience increase, it will become a more useful and practical procedure.

ELECTROCORTICOGRAPHY

An extension of use of the electroencephalogram is its employment in study of the cortical potentials derived directly from the cerebral cortex.[14,15] The technic of the recording is outlined in detail by Penfield and Jasper.[7] The method gives accurate information concerning the electric manifestations of the epileptic discharge. It is of particular use in locating a focus of activity in or near the cortex that may not have been evident in the electroencephalograms from the scalp. For this purpose, electrocorticography has been extensively used in the surgical treatment of epilepsy by Penfield and others.

A further extension of this method has been used by Dodge[16] and others. They have introduced wire electrodes into the cerebrum to a depth of 6 cm. in the area of a suspected focus. The issuing electrodes are anchored to the scalp and incorporated in the dressings. Interval recordings may be made over a period up to seven days, and tracings may be made at operation if deemed advisable. Tracings can be made from areas which show independent electric discharge and which appear to be the primary regions producing electric abnormality. Evidence from such studies can place a lesion several centimeters below the cortical surface and suggest the desirability of a subcortical approach to such a lesion, leaving the overlying cortex relatively intact. This method has been designated "intracerebral" or "depth" corticography.

CHEMISTRY

Since 1920, considerable evidence has accumulated to indicate that chemical changes within the body are intimately concerned in epileptic attacks. Chemical studies were stimulated by the

announcement by Conklin,[17] of Battle Creek, that starvation for two weeks was useful treatment for an epileptic patient. It was thought possible that the disturbance in acid-base balance was responsible for the beneficial effect. Wilder[18] also suggested that the ketone bodies produced during starvation might be anticonvulsant; this will be mentioned again. The fluid balance and the intake and output of inorganic salt were considered significant, as were anoxemia and so on. These factors do not necessarily act separately, and their interaction must be recognized and studied.

Although several useful studies have been made in aimals, the various factors will be considered here from the clinical point of view, for most of the observations have been made on patients.

ACID-BASE EQUILIBRIUM

A number of publications have dealt with acid-base equilibrium. Bisgaard and Noervig[19] stated that they found greater irregularities in the *p*H and concentration of ammonia nitrogen and of total nitrogen in the urine of epileptics than in the corresponding values reported for normal controls. Since their paper was published, evidence has been put forward that this "dysregulation" was not specific for epileptics but occurred in association with food deficiency and other states.

Jarloev[20] was the first to report that the *p*H of the blood tended to be high preceding epileptic convulsions, but his report was brief and contained few data. He gave the *p*H of the blood of normal persons as between 7.3 and 7.34 and stated that the *p*H of the blood of epileptics might be 7.42. Geyelin[21] stated that there was " . . . no *p*H curve definitely characteristic of epilepsy, but that the blood of epileptics showed a distinctly wider range of *p*H from day to day and from hour to hour than did the blood of normal persons." While several other workers published conflicting results, Lennox and Cobb[22] finally concluded that, if the normal range of *p*H was considered to be from 7.3 to 7.5, definite abnormality had not been demonstrated in epilepsy. They agreed that there was an unusual degree of fluctuation from day to day, with a tendency to high values. McQuarrie and Keith[23] studied the blood *p*H in several cases. They employed a modification of Cullen's colorimetric method but used the bicolor standards of Hastings and Sendroy and accepted the normal values given by others as 7.33 to 7.41. The patients studied were living under special conditions, that is, they were following the ketogenic diet, the alkaline ash diet, and so forth, and the results cannot be directly compared with those obtained in other work. There was a tendency, however, for attacks to occur when the *p*H was above the accepted normal.

Studies of the carbon-dioxide combining power of the plasma have been made by numerous workers. Frisch and Fried[24] and others found the carbon-dioxide content to be within normal limits, although Frisch and Fried considered 78.4 per cent to be normal. This is a little higher than the usually accepted figure. Any abnormalities that these authors noted were on the alkaline rather than the acid side.

Gamble and Hamilton[25] did not discover any abnormalities in the acid-base composition of the urine of an epileptic child who was studied continuously for four weeks, during which time she had several periods of seizures. They did find, however, marked increase in the excretion of total acid, total base, and extracellular water during the period when she had the seizures but no change in the urine *p*H or the ammonia. While there have been several further studies that were inconclusive, the work of McLaughlin and Hurst[26] showed that the alkali reserve and *p*H of the blood were slightly above normal, that the value for blood lactic acid was normal, and that there was no demonstrable change in the alkali reserve and the *p*H of the blood just before a convulsion. They showed that the two latter did fall during an attack but that this fall was due to the production of lactic acid and that exactly the same curves could be obtained from a normal subject under strenuous exercise.

Induced alkalosis. Administration of alkalis to some patients may cause convulsions. It is well known that tetany may be precipitated by giving sodium bicarbonate and so forth. Hyperpnea will cause 15 to 50 per cent of epileptics to have convulsions. The mechanism apparently is the production of mild alkalosis by reduction in carbon-dioxide content of the expired air and of the blood. Giving alkali will produce attacks only under certain special conditions, usually when the patients have had a decreased alkali reserve. It has been suggested that it is the sudden swing from so-called "acidosis" to "alkalosis" that precipitates the convulsion. The addition of moderate amounts of sodium bicarbonate to the diet of children who were on the ketogenic diet caused seizures after an interval, particularly if the patients were subject to petit mal attacks. On the other hand, alkali will sometimes help induce ketosis, without causing an increase in convulsions. When patients are not on ketogenic diets or some acid-producing regimen, bicar-

bonate usually will not produce attacks. Frisch and Fried[24] found that they could lower the carbon-dioxide content of the blood and obtain a shift in the *p*H but could not produce attacks.

Induced acidosis. In certain cases, administration of calcium chloride and ammonium chloride has caused a decrease in the number of attacks of epilepsy. Also, in some cases, increasing the carbon-dioxide content of the respired air can decrease the number of attacks. This is a corollary of the fact that overventilation increases the number of attacks. Fasting has been well recognized as a method of decreasing the number of attacks, and it is felt by some that the effect is due to the acidosis present. By others, it is believed that, while acidosis is definitely present, the ketosis which also occurs is the active factor. This was the origin of the ketogenic diet proposed by Wilder[18] and found to be of value, especially in treatment of children.

In summary, then, it may be said that nearly all workers are agreed that the *p*H of the blood of epileptics extends over a rather wider range than does that of normal persons and that there is a tendency of the blood of epileptics toward alkalinity. The attack, however, is not usually a direct function of the *p*H of the blood, although variations may precipitate seizures.

WATER BALANCE OF THE BODY

Following the reports of Fay[27] and McQuarrie[28] in regard to the relationship of water balance of the body to the occurrence of epileptiform seizures, there was considerable interest in hydration, dehydration, and water content of the tissues. A few years previously, studies in water intoxication had been made by Rowntree[29] and associates, who showed that convulsions could be produced by oral administration of large amounts of water, with or without subcutaneous injection of Pituitrin. McQuarrie[28] carried out observations on epileptic children in the same way. He noted increase in the number and severity of attacks when excessive water was retained in the body and reduction in the number or a total disappearance of seizures when the intake and output of water were low. He suggested that, in epilepsy, regulation of water exchange was disturbed with consequent possible hydration of brain tissues. Gamble and Hamilton[25] have shown that the epileptic patient does store water between attacks and excretes this water immediately after a seizure. The fluid is interstitial, and retention of sodium is responsible for the retention of water.

Fay,[27] in a series of papers, called attention to the fact that the convulsive state, whether acute or chronic, is associated with the presence of increased amounts of supracortical fluid within the arachnoid spaces. He suggested, as did McQuarrie,[28] that a low intake of fluid, with some dehydration of the cranial cavity or the brain tissues, might be useful as a therapeutic procedure, and he reported a series of cases in which improvement had taken place under this treatment for periods of one month to two years. He explained the increased amount of fluid on the basis of decrease in absorption of cerebrospinal fluid, occasioned by pathologic changes in the arachnoid and in the pacchionian bodies. He made the following, rather sweeping statement: ". . . supracortical subarachnoid fluid was present in the pathways about the motor areas in conjunction with increased pressure (focal or general) in every mechanism either idiopathic or organic, associated with full generalized or Jacksonian convulsions that I have had the opportunity to study. This comprises the major convulsive state whether acute, chronic idiopathic or symptomatic in origin." Cobb[30] stated that, while abnormal accumulations of fluid in the subarachnoid space are common among epileptic patients, these accumulations cannot result from supracortical increase in pressure and cortical atrophy. He pointed out that fluid flows from the ventricles to the subarachnoid space and that, consequently, pressure must be higher in the ventricles than over the cortex and that there is no known mechanism by which these pressures could become reversed.

A study by Byrom[31] followed very carefully the total exchange of water and salts in epileptics. He found that spontaneous epileptic convulsions were not preceded by changes capable of detection by twenty-four-hour measurements of the net water balance or of the several fractions which compose this balance. He showed that a convulsion was attended by a loss of body weight amounting to as much as 1 kg. and that this loss was due to the extrusion of extracellular fluid, thus confirming Gamble and Hamilton.[25] This output was succeeded by retention of water and some increase in weight. He concluded that the epileptic convulsion is not directly conditioned by the state of hydration of the tissues. Helwig and associates[32] reported death of a patient in convulsions after absorption of 9 liters of tap water given per rectum following cholecystectomy.

McQuarrie and associates[33] studied the effect of water, posterior pituitary extract, and desoxycorticosterone on 2 epileptic patients. Both patients responded satisfactorily to a regimen of desoxycorticosterone, 5 to 10 mg. daily, with an

ordinary mixed diet and some restriction of water intake. This result could possibly be attributed to the specific action of the hormone in causing retention of the sodium and chlorine in the extracellular body fluid, thereby preventing dilution of the latter, as well as increased excretion of water.

In summing up the clinical evidence, then, it may be said that, while the changes in water balance have definite effect in some cases and dehydration may have some therapeutic value, the convulsions are not direct functions of the state of hydration of the brain tissues or of the amount of fluid in the cranial cavity.

INORGANIC SALTS

A few studies of the sodium chloride content of the blood have been made. Hamilton[34] found this normal for 17 patients. Lennox and Allen[35] found it normal for 100 patients and showed that, although reduction in seizures occurred during fasting, administering large amounts of sodium chloride did not cause their recurrence. McQuarrie and associates,[36] in water-balance studies, showed that during the period of freedom from seizures there was a marked increase in the excretion of sodium chloride and during the "convulsive" period the excretion of potassium exceeded that of sodium. They then suggested that there was a change in the permeability of the cells of the nervous system under certain conditions, allowing extra water to enter the cells and diffusion of potassium. This, they felt, might result in increased irritability with convulsions. Smyth and associates[37] found convulsions in dogs to be associated with loss of chloride and resulting alkalosis but felt that the alkalosis was the important factor. McQuarrie and associates[38] studied lecithin, cholesterol, and total fatty acids of the blood in relation to seizures. As the brain is characteristically rich in these substances, this could be of importance. The data favored the view that the mechanism for controlling the semipermeability of the brain cell membranes is inherently defective in epilepsy.

OXYGEN SUPPLY

Lennox[39] has shown that, in certain patients who have attacks of the petit mal type, the attacks can be produced by decreasing the oxygen content of the respired air. If hyperpnea is added to this, the attacks are produced more easily. Conversely, in the oxygen chamber, patients with petit mal have a reduced number of attacks. Lennox and Cobb[40] stated that hyperpnea produces alkalosis, that this causes the blood to give up oxygen less readily than is normal, and that this might be the explanation of the action of alkalosis rather than just the change of *p*H. It has been shown in animals that cutting off the blood supply to the brain for varying periods will cause convulsions; even holding rabbits in vertical position for a time will do the same.

CARBOHYDRATES

The influence of insulin and hypoglycemia in inducing convulsions is well known. The relationship between hypoglycemia and the recurring convulsions of epilepsy is not clear. Perkin and Derbyshire[41] recently published observations on 76 proved convulsive patients whose illnesses were not severe enough to require institutional care. Long-term glucose tolerance tests gave results that suggested frequent abnormality of utilization of carbohydrate. The study was begun by observing convulsive attacks as a result of continued hypoglycemia, with resultant damage to the brain. The question was: How frequently and to what degree do minor and concealed variations in the vital glycogen supply of the brain cell influence the development of the convulsive state? Conclusions could not be drawn, but further investigation of intermediary carbohydrate metabolism seemed indicated.

A most interesting study of spontaneously occurring hypoglycemia in infants with associated convulsions and convulsion-like symptoms recently has been published by McQuarrie.[42] His report concerns 25 patients, all less than 5 years of age with the exception of 1 child. A familial or genetic trait of spontaneous hypoglycemia was seen in 11 of the patients. There were no physical signs diagnostic of this condition, but tests related to glucose and insulin tolerance gave characteristic results. All patients were treated with corticotropin, and all responded favorably.

ADVANCES IN TREATMENT

Advances in treatment of convulsive disorders have developed along 3 lines: (1) An increasing number of anticonvulsant drugs is being discovered. (2) Developments are taking place in use of a ketogenic diet in treatment of children. (3) Surgical excision of brain tissue is being used with increasing accuracy.

Drugs. Bromides were first used one hundred years ago in treatment of epilepsy. Although other drugs have been developed, bromides remain among the more effective anticonvulsant drugs. In 1912, Hauptmann[43] introduced the

use of phenobarbital. This drug is also a very effective anticonvulsant and is of relatively low toxicity. It is probably used today more commonly than any other antiepileptic drug. A modification of this drug, N-methylethylphenylmalonylurea (Mebaral), was introduced in 1932 and is also effective.

In 1938, as a result of testing a large number of drugs for effect in controlling electrically-produced convulsions, Merritt and Putnam[44] recommended administration of diphenylhydantoin sodium, Dilantin, to epileptic patients. This has proved to be a relatively effective anticonvulsant also.

Since 1938, a considerable number of drugs have been introduced, and their effect is gradually becoming understood. These drugs are as follows: methylphenylethyl hydantoin (Mesantoin), trimethadione (Tridione), and paramethadione (Paradione). The latter 2 drugs are essentially effective in the control of petit mal attacks. They may increase the tendency to grand mal attacks.

The list continues with phenacetylurea or phenacemide (Phenurone), metharbital (Gemonil), N-benzyl-β-chloropropionamide (Hibicon), amphetamine (Benzedrine), dextro-amphetamine sulfate (Dexedrine), and N-methyl-α-phenylsuccinimide (Milontin). The latter 3 drugs are mainly of value in the control of petit mal attacks.

In table 1 are listed the various anticonvulsant drugs with initial minimal doses for children. It is emphasized that each drug should be given in increasing amounts until the desired effect is achieved or toxic reaction occurs.

Ketogenic diet. A ketogenic diet is of considerable value in treating children. Keith[45] has reported that 35 per cent of children who took the diet satisfactorily for one to two years remained free of attacks for periods of four to twenty-five years.

To be effective, a ketogenic diet must be rigidly controlled and should be weighed. It is necessary that in the diet the ratio of the ketogenic material to the antiketogenic material be at least 3:1. This ratio is calculated according to Woodyatt's formula in the following manner:

Ketogenic — 90 per cent of fat
46 per cent of protein

Antiketogenic — All of carbohydrate
58 per cent of protein
10 per cent of fat

$$\frac{\text{Ketogenic (or fatty acid)}}{\text{Antiketogenic (glucose)}} \text{ ratio is } \frac{0.90F+0.46P}{C+0.1F+0.58P}$$

The diet is then calculated for the individual patient as follows: The number of calories is 55 per kilogram or 25 per pound of body weight. The amount of protein is set at 1 gm. per kilogram of body weight, which has been found to be satisfactory. The carbohydrate and the fat are then adjusted so that the ratio is as indicated and the calories are satisfactory for nutrition

TABLE 1

Drug	*Initial dose*	*Toxic effects*
Bromide	0.3 gm.	Drowsiness, acneform eruptions
Phenobarbital	16 mg.	Drowsiness, irritability, rash (rarely)
Mephobarbital (Mebaral)	32 mg.	Same
Metharbital (Gemonil)	32 mg.	Same
Diphenylhydantoin sodium (Dilantin)	32 mg.	Ataxia, diplopia, nystagmus, rash, nausea or vomiting
Methylphenylethyl hydantoin (Mesantoin)	50 mg.	Drowsiness, rash, pancytopenia, agranulocytosis
Trimethadione (Tridione)	0.15 gm.	Photophobia, rash, agranulocytosis
Paramethadione (Paradione)	0.15 gm.	Same
Phenacetylurea or phenacemide (Phenurone)	0.5 gm.	Rash, hepatitis, pancytopenia, personality disturbance, albuminuria, leukopenia
Amphetamine sulfate (Benzedrine)	2.5 mg.	Irritability, restlessness, insomnia, tremor
Dextro-amphetamine sulfate (Dexedrine)	2.5 mg.	Same
N-methyl-α-phenylsuccinimide (Milontin)	0.5 gm.	Drowsiness, vertigo, hematuria
5-Ethylhexahydro-5-phenylpyrimidine-4, 6-dione, or primidone (Mysoline)	0.125 gm.	Drowsiness, dizziness, ataxia, rash, disturbed equilibrium
N-benzyl-β-chloropropionamide (Hibicon)	0.5 gm.	Vertigo, ataxia, distress

TABLE 2

Boy, 8 years, 55 lb. (25 kg.) Calories, 1,375					
	25 cal. per lb. body weight		55 cal. per kg. body weight		
	C, gm.	*P, gm.*	*F, gm.*	*Cal.*	*K/AK*
1 day	50	25	119	1,371	1.5
2 days	35	25	126	1,374	2
3 days	20	25	133	1,377	2.7
4 days	15	25	135	1,375	3.1

and growth. The caloric requirement is based on the estimated weight for height, as given in standard tables.

Over a period of four days, the carbohydrate in the diet decreases rapidly and the fat increases (table 2). This is advisable because most children who are placed immediately on the final diet will become nauseated and sometimes vomit severely. However, this very seldom occurs with the indicated plan.

In order to make certain that the patient is in a state of ketosis, a test for diacetic acid is made on the first morning specimen of urine daily. The patient's mother can be taught to do this quite readily. Patients must be kept on this diet in ketosis for six to twelve months. The carbohydrate in the diet is then gradually increased and the amount of fat reduced until the diet is essentially normal again; this usually takes place over a period of three to six months.

Other reported progress. Some other progress has been reported in the results of treatment of epilepsy. There is extensive literature on the subject, but it is difficult to compare results obtained by different persons using different methods. The patient is mainly interested in complete and permanent control of his attacks, and there are few reports of this having been accomplished over long periods.

Nearly fifty years ago, a study of the use of bromides was made by Turner.[46] He stated that attacks of 23.5 per cent of 366 patients were totally arrested for two and one-half to twenty-two years and that 28.7 per cent of the patients were benefited. These statistics were in harmony with other reports at the time.

Arieff,[47] in 1951, gave an excellent report of observations in treatment of 543 patients with epilepsy. He followed patients for ten years and reported that remissions of six months to ten years were produced in 61 per cent of cases by use, as anticonvulsant drugs, of sodium bromide or phenobarbital or the two together. The addition of Dilantin or Mesantoin increased the rate of remission to 68 per cent. Yahr and associates[48] reported studies of 319 patients. With use of Dilantin and phenobarbital, 79 per cent of patients were "controlled" or improved. The addition of other anticonvulsants added 6 per cent, giving an over-all rate of 85 per cent of patients whose conditions were improved or controlled. The patients whose conditions were considered to be controlled were those who were free of seizures for "less than six months up to five and one-half years." The seizure rate of those whose condition was "improved" was reduced at least 50 per cent.

Keith[45] reported the results of treatment of children by means of the ketogenic diet. Results of treatment of 190 patients were satisfactory, and 35.3 per cent of the patients remained entirely free of attacks for four to twenty-two years, although treatment actually lasted only one to three years. Improvement occurred in a further 8.4 per cent. The 190 patients had grand mal, petit mal, or both types of seizures.

Surgical treatment also has been shown to be effective in certain well-chosen cases. Extensive work has been done by Penfield[7] and his associates. Patients were reported in 3 groups: (1) those who underwent cortical excision between 1929 and 1939, (2) those who were treated surgically between 1939 and 1944, inclusive, and (3) those operated on for seizures caused by lesions of the temporal lobe from 1939 to 1949, inclusive. Patients of the first group were followed for one to eleven years, and 43 per cent were found to have been successfully treated, that is, they had had no seizures after operation or they had had 1 or 2 attacks before cessation of seizures. Patients of the second group were followed for one to seven years, and 56 per cent were found to have been successfully treated. Patients of the third group were followed for one to eleven years, and 53 per cent of those who had been subjected to excisions were considered to have had a successful result.

From the over-all point of view, it seems reasonable to say that control of seizures for as long as twenty-two years can be obtained in more than 65 per cent of cases by use of medication or the ketogenic diet. This percentage

may be increased if the special group in need of surgical care is added.

It is impossible to say, of course, when a patient subject to epileptic attacks is cured. Turner[46] and Reynolds[4] found that, after a patient had been free from attacks for more than eight years, relapses rarely occurred. Keith[45] noted that 49 of 67 patients who were considered "well" had been free from attacks for nine years or more. This was 73.1 per cent of all patients who were classified as well and 25 per cent of the group of children treated by the ketogenic diet. It seems possible that, as a result of intensive pharmacologic studies, other drugs having a more intense and prolonged anticonvulsant effect may be discovered. It is probable, however, that the final solution to the control and cure of convulsive disorders will depend on a more intimate and extensive knowledge of brain tissue and of functioning nerve cell.

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Parapertussis

WILLIAM L. BRADFORD, M.D.
Rochester, New York

Parapertussis is a relatively mild respiratory tract infection caused by *Hemophilus parapertussis*. The organism was first described in 1937 by Eldering and Kendrick[1] and by Bradford and Slavin.[2] In each instance it was identified from cultures taken from suspected cases of whooping cough. In 1941 Miller and associates[3] stated that in all probability 2 strains of the organism had been isolated in Copenhagen in 1933, although they were not at the time recognized as such. Because of the green cast produced by their growth in Bordet-Gengou medium containing horse blood, they were called the "Green Strains" and were later studied by Krarup. In 1934, 2 additional strains were isolated, 1 of which was later identified by Eldering as *Bacillus parapertussis*.

Since 1937, the organism has been identified in such widely distant areas as England, Denmark, Mexico, and in the United States from California, Virginia, Kentucky, and Illinois. It has been the subject of considerable interest to bacteriologists because of its close antigenic relationship to *H. pertussis* and *Brucella bronchiseptica;* and to clinicians because the disease it causes so closely resembles whooping cough. Because it can be differentiated from whooping cough only by cultural methods, and because no cross immunity exists between the 2 diseases, it is important in the correct interpretation of the value of pertussis vaccine.

INCIDENCE

Very little is known in regard to the true incidence of parapertussis. In our original study[2] in 1937 we encountered 8 strains of the organism in a series of 160 consecutive positive cultures reported by the Health Bureau Laboratory, representing 5 per cent of the proved cases.

Eldering and Kendrick[4] in 1952 reported their findings over a sixteen-year period, 1935 through 1950. Of 22,135 diagnostic cultures examined for both organisms, they observed 4,483 positive specimens, of which 106 were parapertussis and 4,377 were pertussis; representing, respectively, 0.5 and 19.8 per cent of the total specimens. The positive parapertussis cultures were from 65 patients or 2 per cent compared with 3,263 pertussis patients. During this period, 6,270 cases of whooping cough were reported from the area.

The largest group of cases were reported in 1954 by Lautrop[5] from Copenhagen. It consisted of 256 cases observed from November 1950 to March 1952. From November 1950 to May 1951 the infection prevailed in epidemic form, according to Lautrop. *H. parapertussis* was found in 5 per cent of all cultures examined, representing 16 per cent of all positive cultures. He estimated the total number of parapertussis cases in Denmark during this period to have been between 50 and 250 thousand.

In a recent report[6] from England, the parapertussis organism was isolated from 24 children compared to 482 with *H. pertussis* infection.

The occurrence of humoral agglutinin versus *H. parapertussis* in the general population has been cited as evidence that the infection is fairly widespread. Miller[3] found them in 40 per cent of the children examined in San Francisco with negative histories for parapertussis, pertussis, and pertussis vaccine. In a study of 10 proved cases of parapertussis, he found that specific agglutinins developed as a result of the infection and persisted for as long as forty months.

Flosdorf and associates[7] reported that 61 per cent of a group of Philadelphia children had agglutinins.

In a recent study[8] of 531 serums representing

TABLE 1
SHOWING SERUM AGGLUTININ TITERS AGAINST *H. PERTUSSIS* AND *H. PARAPERTUSSIS* IN 531 CASES

	Distribution of cases according to titer										
Antigen	0	10	20	40	80	160	320	640	1280	2560	% > 320
H. pertussis	144	5	32	34	83	50	78	83	12	10	34.4
H. parapertussis	203	46	73	57	75	39	24	7	6	1	7.1

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

TABLE 2

ABSORPTION TESTS. RELATIONSHIP OF *H. PARAPERTUSSIS* AND *H. PERTUSSIS*

Antiserum	*Absorbing antigen*	*Before or after absorption*	*H. parapertussis*	*H. pertussis*
Parapertussis		Before	2560	10
	H. parapertussis	After	0	0
	H. pertussis	After	1280	0
Pertussis		Before	80	5120
	H. pertussis	After	0	0
	H. parapertussis	After	0	1280

Showing poor absorption of homologous agglutinins by heterologous antigen; and conversely, good absorption of heterologous agglutinins by homologous antigens.

a random sample of admissions to our pediatric service, 328 or 61.7 per cent were found to possess agglutinins against *H. parapertussis;* 7.1 per cent with titers greater than 1:320 (table 1). In a group of 88 children with negative histories of pertussis and of pertussis vaccine, 42 or 47.7 per cent had agglutinin titers above 1:10.

THE ORGANISM

The name *B. parapertussis* was given to the organism by Kendrick[9] in 1938 who objected to its inclusion in the hemophilic group because it possesses certain antigenic properties common to *Br. bronchiseptica* as well as to *H. pertussis.* Morphologically, *H. parapertussis* is almost identical with *H. pertussis.* When first isolated, each is a short coccoid bacillus about 0.5 μ in length.

After 48-hours growth on B-G medium, the colonies of *H. parapertussis* are larger and the zone of hemolysis is darker. It produces a brown discoloration on potato, Levinthal's agar, and in peptone medium. This results from a change in the iron-containing factor of the medium, probably augmented by the alkalinity resulting from its growth.

Biochemically, the organism is relatively inert, fermenting no sugars and producing no indol. Unlike *H. pertussis,* it utilizes citrate and splits urea.

Serologically, *H. parapertussis* possesses at least 2 minor antigens in common with *H. pertussis.* According to Flosdorf, these are responsible for cross-agglutination between the organisms. By absorption tests (table 2) it is clear that the homologous agglutinins are not well absorbed by the heterologous antigen, but the heterologous agglutinins are absorbed by the homologous antigen.

Studies of the antigenic structures of the 2 organisms suggest similarity. As in the case of *H. pertussis,* there appears to be at least 3 antigenic components of *H. parapertussis;* an agglutinogen, a heat labile, and a heat stable toxin. We[8] have found that the skin reactions of infants to the agglutinogen fraction changes from negative to positive after active immunization with vaccine containing killed *H. parapertussis* (table 3).

The toxin is similar to, but less potent, than that of *H. pertussis* (Bruckner and Evans,[10] 1939). Flosdorf stated that the heat labile toxin content of the organism is about one-tenth that

TABLE 3

SHOWING AGGLUTININ TITER AND SKIN REACTIONS OF 10 INFANTS BEFORE AND AFTER INJECTION OF VACCINE CONTAINING *H. PARAPERTUSSIS*

AGGLUTININ TITER		SKIN REACTION IN MM (FRACTION III)	
Before vaccine	*After vaccine*	*Before vaccine*	*After vaccine*
10	320	0	15
20	160	3	30
0	640	3	5
0	320	2	20
0	80	2	12
0	320	0	20
80	320	0	40
20	640	0	20
20	640	3	8
10	80	5	20

of *H. pertussis*. According to Bruckner and Evans the toxins of both *H. parapertussis* and *Br. bronchiseptica* were neutralized by pertussis antitoxic serum. Their role in immunity and pathogenesis of the infections is not clearly defined.

Immunity. It is not known that an attack of parapertussis confers lasting immunity. Proved instances of second attacks have not yet been reported. There is no cross immunity with pertussis and pertussis vaccine does not protect against parapertussis. We have observed 9 instances of bacteriologically proved cases of parapertussis occurring in children well immunized against pertussis. However, Flosdorf has suggested the theoretical possibility that enough of the common minor antigens present in *H. pertussis* vaccine might be given to afford at least some protection against parapertussis.

Virulence. In mice, experimental infection is easily produced by intranasal or intratracheal inoculation. It is characterized by moderate leukocytosis and by pulmonary lesions resembling those produced by *H. pertussis* (Bradford and Wold,[11] 1939). When inoculated intracerebrally into mice, the organism is relatively avirulent compared with *H. pertussis*.

Clinical picture. The incubation period of parapertussis is from six to fifteen days. The onset is similar to that of whooping cough, but may be somewhat more abrupt, occasionally resembling tracheitis. The cough, though spasmodic and sometimes followed by a whoop, is less severe. Vomiting is less frequent and the entire course is often no more than two or three weeks. Complications are rare although two fatal cases of pneumonia were reported by Zuelzer and Wheeler[12] in 1946.

Therapy is usually symptomatic. *H. parapertussis* is susceptible[13] in vitro and in vivo to Terramycin, chloramphenicol and Aureomycin, which may be administered when indicated (figure 1). Although it has been suggested[14] that active immunization be used by combining *H. parapertussis* with *H. pertussis* into a vaccine, at the present time neither the incidence nor the severity of the infection in this country is great enough to justify this procedure.

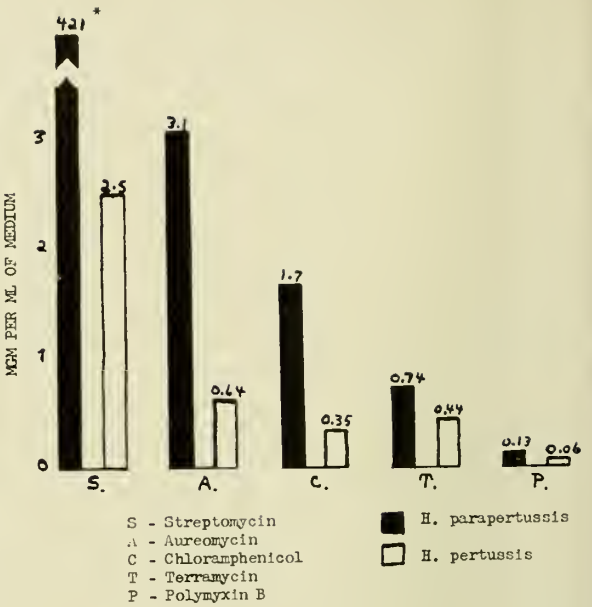

Fig. 1. In vitro action of antihiotics versus *H. Parapertussis* and *H. Pertussis.*

SUMMARY

A brief account of the history, incidence, causative agent, and pathogenesis of parapertussis has been given. Frequent comparison with *H. pertussis* and whooping cough justifies the conclusion that the chief importance of parapertussis in this country at the present time lies in its close clinical and immunologic relationships to pertussis and not as a public health problem.

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Lancet Editorial

A Tribute to Dr. Irvine McQuarrie

For many years the May issue of Journal-Lancet has been devoted primarily to papers of special pediatric interest. Therefore, by tradition it has come to be regarded by its readers, publishers, and editors alike as the "Pediatric Number" of the year.

Serving as the official journal for the Northwestern Pediatric Society as it does, Journal-Lancet ordinarily derives many of its manuscripts for publication from the annual scientific meeting of the society. When available for publication, the manuscript used by the guest speaker at the annual meeting of the organization is published as the leading article of the issue.

The customary pattern of publication has been followed again this year, but in a much more grandiose version than usual, because of the great profusion of excellent papers available to us from a joint meeting of the Northwestern Pediatric Society and the department of pediatrics, University of Minnesota. The papers for the present issue were selected by members of Journal-Lancet's editorial board from among the 40 odd original manuscripts prepared especially for the scientific program held in connection with the Pediatric Grand Reunion on September 22, 23, and 24, 1954, to celebrate the twenty-fifth anniversary of Dr. Irvine McQuarrie's service to the University of Minnesota as head of the department of pediatrics.

The primary objectives in selecting papers for this particular issue were (a) to provide articles of general interest that would satisfy the tastes of all of our readers, (b) to insure a reasonable balance between the theoretic and the practical aspects of the pediatric field, and (c) to appraise advances in the field during the past third of a century and to indicate the new directions which original investigations are taking. Many of the other titles submitted for the program were of equal interest but were not even considered for inclusion merely because of lack of space. It is expected that most of them will appear individually in subsequent numbers of Journal-Lancet and all papers on the program are to be published together in a single volume, commemorating the occasion.

The editorial board members of Journal-Lancet take unusual pride in the extraordinary accomplishments of Irvine McQuarrie. We welcomed this opportunity to join in the celebration of his twenty-five years of service as chief of the department of pediatrics, University of Minnesota, where his contributions and influence for betterment of child health became worldwide.

J. Arthur Myers, M.D.

Editor's Note

This issue of Journal-Lancet, one of the largest in history, is not big enough to accommodate all of the papers selected for this Pediatric number. It is with regret that we had to postpone publication of two outstanding papers:

The article, "A Clinical and Experimental Study of Agammaglobulinemia" by Robert A. Good, M.D., and Richard L. Varco, M.D., will appear in the June issue and the article, "The Role of the Pituitary-Adrenal System in Rheumatic Fever" by Vincent C. Kelley, M.D., has been scheduled for the July issue.

The Physiological Basis of Medical Practice, by Charles Herbert Best, M.D., and Norman Burke Taylor, M.D., 1955. Baltimore, Maryland: The Williams & Wilkins Co. Sixth edition. $12.00.

The authors have been helping to educate medical students and to keep practitioners up-to-date in physiology for almost 2 decades. Every year or two since the first edition in 1937, a reprint or new edition has been published, the sixth this year, 1955. Meanwhile, 4 Spanish and 2 Portuguese editions have been issued.

The fourth edition had 1,058 pages of text and 111 pages of references and index. The fifth edition had 1,330 pages in all, and the current sixth edition has 1,224 pages of text and 133 of references. In spite of the greater number of pages, the sixth edition is less bulky than the fifth because of the lighter paper stock used.

The preface states that this is the most extensive revision since the first edition by elimination of old material and replacement by new. The authors have heeded all worthy corrections and suggestions received from readers of previous texts, and have adhered to their original objective of emphasis upon disorders and treatment of human diseases. That is, the endeavor has been to link the laboratory and clinic. The title, *The Physiological Basis of Medical Practice,* has been strictly and consistently the framework and reference for their presentation.

This work will continue to be, as it has been in the past, good for the student and the practicing physician to have at hand to supply basic physiologic data useful for understanding normal bodily function and interpreting the abnormal activities which produce clinical manifestations of disease.

James B. Carey, M.D.

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The Management of Mental Deficiency in Children, by I. Newton Kugelmass, M.D., 1954. New York City: Grune and Stratton. 312 pages. $6.75.

This book is the best thing that we have seen on mental deficiency in children. Kugelmass writes well, clearly, and to the point. He discusses the many different types of mental abnormality due to different causes. This book should be in every medical liberary and in the office of every pediatrician. It is written in such simple English that it also might be of value to the parents of retarded children. The chapter on the management of the retarded child is excellent and this is so well written that parents could benefit a great deal from it.

An interesting section is included on the several types of mental injury that are due to chemicals in the blood which are not properly metabolized.

Walter C. Alvarez, M.D.

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Surgery of the Adrenal Glands, by William Wallace Scott, M.D., and Perry B. Hudson, M.D., 1954. American Lecture Series, American Lectures in Abdominal Viscera, edited by Lester R. Dragstedt, M.D. Springfield, Illinois: Charles C Thomas. 150 pages. $3.50.

This attractive little volume written by men who have accumulated a broad experience in the field of adrenal surgery should be of considerable value to the surgeon who has only occasional contact with this field. Although the dramatic nature of the clinical manifestation of adrenal tumors has given rise to many papers on all aspects of the subject, they are rather diffusely spread throughout the medical literature and no comprehensive monograph on the surgical aspects of this subject has been published since Hugh Young's book which is now only of historic interest.

Drs. Scott and Hudson have done a considerable service, therefore, in reporting in a single volume the significant chemical and physiologic aspects of the subject along with the clinical manifestations of adrenal disease and descriptions of the surgical approaches. The first 3 chapters are devoted to a very brief discussion of structure and function including only the very minimum discussion of the various adrenal substances with their physiologic action. The main body of the book is devoted to tumors of the adrenal gland, both cortical and medullary, functional, and inactive. The clinical entities of hypertension caused by pheochromocytoma, adrenogenital syndrome, and Cushing's syndrome are considered in detail. Perhaps the most valuable aspect is the rather detailed descriptions of some methods. These include the interpretation of the different ketosteroid fractions of the urine, the performance and interpretation of the tests for pheochromocytoma, and the technic of presacral perirenal air insufflation. In addition, rather specific directions are given for the support of patients operated upon for Cushing's syndrome and pheochromocytoma. These measures which are of the utmost importance in surgical management are frequently difficult to extract when needed from the current literature. The last 2 chapters deal with surgical approaches and bilateral adrenalectomy for disseminated breast and prostatic cancer.

This is a rapidly changing field and the authors deserve credit for their courage in preparing the book at a time when our understanding of adrenal physiology and adrenal disease is progressing so rapidly. A few very significant contributions such as the elucidation of the salt-regulating hormones of adrenal have taken place since the manuscript was prepared. Such developments, however, have little to do with the basic arguments and the therapeutic considerations in this book.

Bernard Zimmermann, M.D.

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Doctor in the House, by Richard Gordon, 1953. New York: Harcourt, Brace & Co. $2.75.

Two years ago a 30-year-old London doctor, under the george spelvin of Richard Gordon, wrote *Doctor in the House* on a cargo ship en route from London to New York. It is an hilariously funny tongue-in-cheeker with just enough truth in it to tickle the doctor who has a streak of cynicism in his makeup. The dialogue is as British as a privet hedge, but the high jinks of the medical students through five years of training at St. Swithin's hospital could survive transplanting. The book bubbles with gaiety and gentle humor. High spirits prevail and it is plain to be seen how the film producers of England have made it into a picture. If you enjoy *Punch* and shortbread, Navy Cut smoking tobacco, and Alex Guinness and appreciate the contrasts between the customs and inner attitudes of these two English-speaking peoples, you'll have fun out of the original style and wacky wit of *Doctor in the House.*

Maurice Wolff

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American College Health Association . . .

NEW MEMBERS

We are happy to welcome 2 new members whose applications have been approved by the Executive Committee:

Long Beach State College, 6201 East Anaheim, Long Beach 4, California. Representative: Francis J. Flynn, Ed.D.

New Haven State Teachers College, 501 Creseent Street, New Haven 15, Connecticut. Representative: Hilton C. Buley, Ed.D.; alternate: Dorothy R. Granoff, M.D.

SECTION ACTIVITIES

The Illinois regional section offieially ehanged their eonstitution at the annual meeting held Deeember 4, 1954 at Roosevelt University so that the name of the organization is now "Illinois College Health Association."

The following offieers were eleeted: President, Mrs. Raidie P. Merdinger, R.N., Roosevelt University, Chicago; vice-president, Dr. James L. Weiler, Knox College, Galesburg; secretary-treasurer, Dr. L. M. Dyke, University of Illinois, Urbana; eouneil member (two years), Dr. W. C. Hardy, Normal University, Normal.

The other 2 members of the Exeeutive Council are the past president, Dr. William Lester, Jr., University of Chicago, and Mrs. Margaret Hartzo, R.N., Lake Forest College.

A motion was passed that the Exeeutive Counеil be requested to take whatever steps are neeessary to lead to the organization of a regional grouping of Illinois and Indiana members of the A.C.H.A. A letter has been sent from the Illinois Seetion to the colleges and universities in Indiana which are members of the A.C.H.A. suggesting formation of a joint committee from Indiana and Illinois to prepare reeommendations for presentation to a joint meeting in the fall.

Speakers at the Deeember meeting of the Illinois seetion included Dr. Henry Poncher, director of the Student Health Service at Valparaiso University, Valparaiso, Indiana, whose topie was, "What Should Be the Funetion of a College Health Service," and Dr. Edward Sparling, president of Roosevelt University, Chicago, who addressed the meeting on the subjeet, "Health as an Objective of a College Education."

A Round Table which was devoted to the explanation of new methods and ideas pertaining to the development of mental health programs in colleges was held the evening of May 10 at the meeting of the Ameriean Psyehiatrie Association in Atlantie City, New Jersey. Dr. Dana L. Farnsworth of the Department of Hygiene of Harvard University was the chairman. The general title of the program was "New Directions in College Mental Health." Participants ineluded Bryant M. Wedge, M.D., Yale University, "Researeh and Personality Development;" A. A. Hellams, M.D., Mental Health Division, State Department of Health, Oklahoma, "Mental Health at Wholesale;" William Brill, M.D., University of Nebraska, "Psyehiatric Screening of Teaeher Candidates;" Preston K. Munter, M.D., Massaehusetts Institute of Teehnology, "Group Aetivities as a Supplement of Psyehotherapy;" and Clifton C. Rhead, Jr., M.D., University of Chicago, "Interrelationship Between Group Aetivity and Personality Funetions."

(Continued on page 34A)

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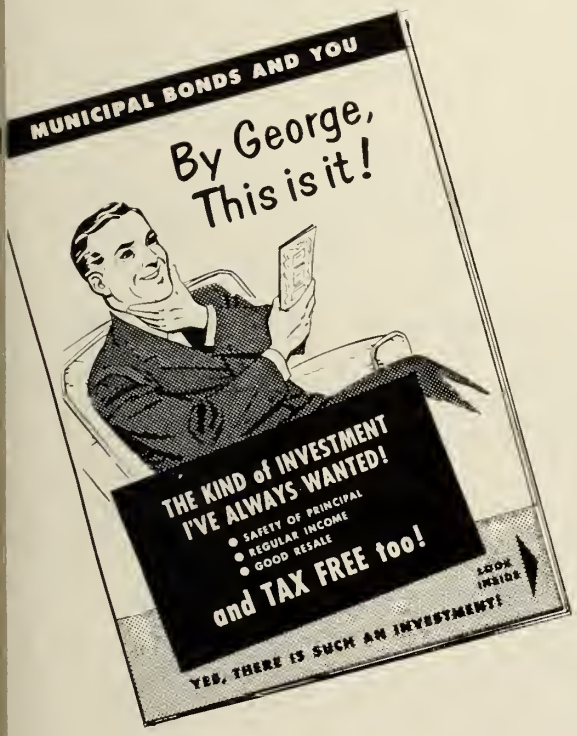

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TABLE 1

INCIDENCE OF POSTPARTUM HEMORRHAGE

Years	Number of vaginal deliveries	Number of hemorrhages	Per cent
1926 to 1935	5,495	257	4.6
1936 to 1945	12,248	640	5.2
1946 to 1952	6,827	305	3.1

jected to the use of intravenous ergonovine because it rarely produces a transient elevation of blood pressure. In the University of Iowa hospitals, intravenous ergonovine has been employed for several years and no ill effects have been attributed to its use.

An objection which has often been raised against the use of intravenous ergonovine before the completion of the third stage of labor is the increased necessity for manual removal of a placenta which has become incarcerated above a contraction ring. Diddle[3] employed intravenous ergonovine in a series of 1,960 patients with an incidence of manual removal of 0.5 per cent, and Davis and Boynton[2] employed the same oxytocic in a similar manner with an incidence of 0.8 per cent. Martin and Dumoulin[6] found in a controlled series of 1,000 cases that intravenous ergonovine increased the number of manual removals from 1.1 to 3 per cent. These same authors reported an incidence of manual removal of 1.6 per cent in 77,858 deliveries in various English hospitals when no intravenous oxytocic drug was used. Probably oxytocics given early in the third stage do not increase the number of manual removals. However, if the number were increased, no great complication of labor would occur, and the benefits derived would more than compensate for any inconvenience caused by a retained placenta. During the past few years our hospital has adopted a policy of more active interference in the management of the third stage of labor. A third stage of twenty minutes or any unusual bleeding before the placenta has separated are indications for immediate manual removal. Until recently most physicians taught that the uterus must never be invaded unless absolutely necessary. A fear of invading the postpartum uterus was instilled into the profession largely because of the reported high maternal mortality from such a procedure. The advent of antibiotics and the greater availability of blood have done much to lower the hazards of intrauterine manipulations. However, the most important factor in removing this fear has been the final realization that the invasion of the postpartum uterus has not been the cause of a high mortality but rather the delay of the procedure until the patient was in shock from a considerable loss of blood. Today manual removal of the placenta is felt to be a safe procedure if done when the patient is in good condition and under aseptic conditions.

In the University of Iowa hospitals, there have been 210 manual removals of the placenta in 27,039 deliveries or 1.25 per cent. There was an increase in the incidence during the years 1942 to 1954 (table 2), approximately 3 times that which occurred in the years 1926 to 1942. Indications for manual removal became more lenient during the second period, especially the last two years when the incidence was 2.2 and 3.5 per cent respectively. It should be emphasized that the decrease in the incidence of postpartum hemorrhage parallels the increase in the number of manual removals of the placenta performed.

The most common indications for manual removal are unusual bleeding and prolongation of the third stage (table 3). The amount of bleeding which should be permitted before manual removal of the placenta is justified is not definitely defined in most hospitals. In our clinic a manual removal is done when the patient has lost as much as 200 cc. of blood and the placenta cannot be delivered by simple expression. The matter of the duration of the third stage of labor in the absence of bleeding, before manual removal is justified, is not a settled issue. Certainly, any prolongation to one or two hours, as was frequently done in previous years, should not be permitted at the present time. A long third stage usually means a slow loss of blood which appears to be insignificant at the time but over a considerable period may prove to be

TABLE 2

INCIDENCE OF MANUAL REMOVAL OF PLACENTA

Years	Number of deliveries	Number of manual removals	Per cent
1926 to 1942	15,824	70	0.44
1942 to 1954	11,215	140	1.25
Total	27,039	210	0.78

TABLE 3

INDICATIONS FOR MANUAL REMOVAL OF PLACENTA

Indication	1926 to 1942 Number of cases	1926 to 1942 Per cent	1942 to 1954 Number of cases	1942 to 1954 Per cent
Hemorrhage	34	48.5	39	27.9
Prolonged third stage	28	40.0	60	42.8
Prophylaxis	8	11.3	9	6.4
Teaching	0	0.0	32	22.8
Total	70	100.0	140	100.0

exsanguinating to the patient. In our clinic the placenta which has not separated within twenty minutes is removed manually. This procedure has an advantage in that removal can usually be done while the patient is under the same anesthesia used for the delivery of the baby and the repair of lacerations and episiotomy. Some placentas have also been removed prophylactically to prevent hemorrhage in prolonged labors and in some of the mild placenta previas which were treated by vaginal delivery. It is also felt that medical students, interns, and residents should be taught the technic of manual removal as well as the principles of other obstetric procedures. With this in mind, we have done several manual removals in the last few years for teaching purposes. At least the younger physicians who are trained in the clinic will go into practice and have no fear of invading the postpartum uterus as many of the older physicians do even when indication for the procedure is urgent.

A definite increase occurs in the morbidity of puerperal patients after the placenta is removed manually (table 4). In the second period of years the incidence of morbidity was less than half of that which it was during the first period, when patients were often allowed to lose considerable blood before manual removal of the placenta was felt indicated. The total mortality of 210 manual removals of the placenta was 2 (table 5). In 1 patient death was due to an obstetric complication which had no relation to the manual removal of the placenta. The other patient died not because of the manual removal but because the procedure was postponed for several hours, or until she had become exsanguinated and had developed a severe degree of shock. In modern obstetrics there is no reason why any patient's life should be sacrificed because of a manual removal if the procedure is done under aseptic conditions and before the patient has lost a considerable amount of blood.

A patient who bleeds after the third stage of labor should be given some intravenous oxytocic if such a drug has not already been administered recently. Repeated frequent injections of oxytocic drugs are ineffective and should not be employed. The uterus should be brought up out of the pelvis and should be vigorously massaged against the promontory of the sacrum. If these procedures do not immediately control the bleeding, the lower birth canal should be inspected for lacerations. The cervix should be brought into view by means of traction with ring or ovum forceps, and the vaginal fornices should be carefully examined for lacerations. If the bleeding seems to be coming from the uterine cavity, the entire endometrial surface should be palpated for any rupture of the uterine wall or for any placental tissue. If the bleeding is not due to retained secundines or to some type of laceration, it is the result of uterine atony. The matter of packing to control bleeding is highly controversial. Packing the vaginal canal and uterine cavity solidly with gauze may prevent atonic bleeding and does little harm. However, packing more than once proves to be ineffective and also quite traumatic to the vaginal mucosa and is to be condemned. If a uterine pack does not prevent bleeding, an abdominal hysterectomy should be undertaken. The uterine arteries should be isolated and ligated and if this procedure fails to control bleeding, a rapid subtotal hysterectomy should be performed.

In a recent study of 640 postpartum hemorrhages, 600 cc. or over, we found that approximately 9 out of 10 patients bleed because of atony of the uterus (table 6). Most atonic bleeding can be prevented by the administration of intravenous ergonovine at the time of the delivery of the shoulders of the baby and by the elimination of heavy inhalation anesthesia. Atonic bleeding should be anticipated in prolonged labors and in those conditions in which the uterus is overdistended such as a twin pregnancy, an oversized fetus, and hydramnios.

TABLE 4

MORBIDITY IN MANUAL REMOVAL OF PLACENTA

Period		*Number of manual removals*	*Number of morbid cases*	*Per cent*
1926 to 1942		70	29	42.0
1942 to 1954		140	24	17.2
	Total	210	53	25.2

TABLE 5

MATERNAL MORTALITY IN MANUAL REMOVAL OF PLACENTA

Period		*Number of manual removals*	*Number of deaths*	*Per cent*
1926 to 1942		70	2	2.8
1942 to 1954		140	0	0.0
	Total	210	2	0.9

TABLE 6

ETIOLOGY OF POSTPARTUM HEMORRHAGE

Cause of hemorrhage	*Number of cases*	*Per cent*
Uterine atony	579	90.5
Retained placenta or placental parts	29	4.5
Birth canal lacerations	27	4.2
Secondary to episiotomy or to plastic repair after delivery	5	0.7
Total	640	99.9

Some of the most severe and often fatal cases of postpartum bleeding are the result of uterine rupture or lacerations of the birth canal. These can be prevented to a great extent by the elimination of traumatic and difficult deliveries. At the present time, delivery by cesarean section is much safer for both mother and baby than some traumatic vaginal procedure such as difficult forceps or internal version and extraction. Use of intravenous Pitocin to initiate or stimulate labor has caused some fatal cases of postpartum bleeding due to uterine rupture. Simple rupture of the membranes is preferable and is the most effective, least harmful, and simplest method we have for initiation of labor. Intravenous Pitocin should only be used to stimulate labor in primiparas who are having a prolonged labor of over thirty hours from primary uterine inertia. The drug should not be employed in multiparas, in patients with secondary uterine inertia, or in those who have cephalopelvic disproportion or an abnormal presentation. The patient should be carefully and continuously observed by a physician so that any abnormal uterine action can be detected and the drug stopped in time to avert a disaster. Because of the increased popularity of intravenous Pitocin by some physicians, probably some maternal deaths in the future will be caused by its injudicious use under poorly controlled conditions.

Of great importance in the management of the third stage of labor is alertness on the part of the attending physician. He should always anticipate hemorrhage, do everything possible to prevent it, and take adequate steps to treat it if it occurs. The reviewing board of the Iowa State Mortality Committee in its two years of existence has found that certain precautions need to be emphasized to the medical profession. Physicians often do not recognize hemorrhage as a cause of death. Shock, embolism, or cardiac failure are frequently given as the cause of death when the real reason for the fatality has been loss of blood. Naturally, if the exact cause of death is not recognized, proper treatment cannot be instituted. The treatment of postpartum hemorrhage is frequently delayed too long. Too often the physician waits until the patient's pulse becomes rapid or her blood pressure falls to a shock level before he becomes aware of the gravity of the situation. Often when these signs are present a fatal catastrophe cannot be averted. Doctors tend to underestimate the amount of bleeding during the third stage, especially when the loss of blood is slight over a long period of time. A good rule to follow is to estimate the amount of blood to be lost in a given patient and this doubled will be approximately the correct amount to be transfused. Plasma expanders and blood substitutes are used too frequently. These should only be employed to tide the patient over until matched blood becomes available. There can be no permanent substitute for blood in the treatment of postpartum hemorrhage. Hemorrhage during the third stage should be anticipated, and in these cases saline or dextrose should be running into the vein of the patient through a large bore needle at the time of delivery so that blood can be given immediately if necessary. Whenever trouble in the third stage can be foreseen, 1 or 2 units of matched blood should be available. Physicians often fail to request or seek consultation quickly enough when confronted with a severe postpartum hemorrhage. Whenever bleeding in the third stage cannot be promptly and completely controlled, the most competent assistance should be sought immediately.

CONCLUSION

The fact that postpartum hemorrhage is today the most common cause of maternal deaths must be emphasized. Deaths from hemorrhage can almost always be prevented. In the future doctors should do everything possible to prevent postpartum hemorrhage and must be prepared to treat it adequately. Much can be accomplished by employing a more active management of the third stage of labor than has been used in the past, by the administration of intravenous ergonovine with the birth of the fetal shoulders, by the elimination of traumatic deliveries and the injudicious use of Pituitrin, and finally by discarding heavy inhalation anesthesia.

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Venous Mesenteric Thrombosis Associated with Pregnancy

RALPH E. LEIGH, M.D., and ROBERT H. DE LANO, M.D.
Grand Forks, North Dakota, and Northwood, North Dakota

Mesenteric thrombosis is a condition both unusual and interesting. The textbooks on surgery treat the subject very sparingly, usually under the heading of one of the etiologic factors of intestinal obstruction and generally comment on its rapidly fatal outcome.

Vascular mesenteric occlusion is divided into 2 main categories: (1) arterial vascular occlusion which is usually secondary to valvular diseases of the heart, and (2) venous mesenteric occlusion usually considered secondary to (a) recent surgery, (b) splenic disease, and (c) trauma to the abdomen. The remarks in this paper are directed toward venous occlusion.

In 1913, L. B. C. Trotter[1] collected 360 cases from the literature and reported 7 new cases. Of these cases, 60 per cent were arterial and 40 per cent venous in origin.

In all the collected papers of the Mayo Clinic, the only reference to the subject is an abstract of a thesis by James A. Wilkens[2] in volume 15, published in 1923. He dealt largely with arterial occlusion. Wilkens added 35 cases from the records of the Mayo Clinic and the University of Minnesota. Of these, 8 showed mesenteric venous thrombosis. He concluded that the condition always requires surgery.

In Trotter's accumulated cases, 3.6 per cent were diagnosed before death. In Wilken's series of 35 cases, 4 or 11.4 per cent were diagnosed before operation or death. He also observed that the size and location of the infarct does not necessarily bear a direct relation to the severity of the symptoms.

In 1940, Marion L. Mathias[3] observed that mesenteric thrombosis occurs more often than is usually believed. He reported a case of a patient on whom resection of the gangrenous bowel was performed. Both ends were exteriorized but anastomosis was not done because of the patient's serious condition. This patient died on the sixth postoperative day. He reported a second case of a patient in whom a primary anastomosis was done who survived surgery.

Owen Wangensteen[4] devotes a chapter to vascular causes of intestinal obstruction in his book Intestinal Obstructions. He reported a case of a patient diagnosed on his service who survived surgery.

In 1942, Henry Giamarino and Samuel A. Jaffe[5] reported the case of a 38-year-old male who survived operation. They surmised recovery was due to the fact that (1) the condition was venous occlusion, (2) diagnosis was made and operation performed early, (3) postoperative care was careful, and (4) no complicating illness occurred.

Josephus C. Luke[6] in 1943 reported a successful operation on a patient who was treated with heparin postoperatively. Paul F. Fox[7] in 1944 reported a successful surgical case of a patient treated postoperatively with dicumarol.

In 1950 J. O. Nolan and L. A. St. John[8] reported 2 cases of vascular occlusion, 1 of which was fatal. The other was explored but not resected. However, involvement of the transverse colon was present in the surviving patient. In this case, collateral circulation might explain the fortunate outcome.

In 1950, Haggstrom and Rousselot[9] reported a review of 76 patients admitted to St. Vincent's Hospital, New York City, in the years 1947 and 1948. Of these, 4 had mesenteric thrombosis and died. E. L. Strohl and Jack Lasner[10] reported in 1950 a case of a 53-year-old man who suffered 2 episodes of mesenteric vein thrombosis. He survived both operations; resections were performed at each operation.

John P. North and Oscar J. Wollenman, Jr.,[11] in 1952 reported 3 cases seen in a two-year period at McKinney Texas Veterans Hospital. They feel the condition occurs more frequently than is usually recognized and that exploratory

RALPH E. LEIGH, *a 1925 graduate of the University of Minnesota Medical School, is on the staff of Deaconess and St. Michael's hospitals, Grand Forks, North Dakota, and head of the department of obstetrics at the University of North Dakota School of Medicine.* ROBERT H. DE LANO, *a 1952 graduate of Vanderbilt University, is on the staff of Deaconess Hospital, Northwood, North Dakota, and courtesy staff of Deaconess Hospital, Grand Forks.*

laparotomy may be the only means of establishing a diagnosis sufficiently early to permit successful resection.

In 1950, Richard J. Chodoff[12] reported the case of a 68-year-old man in whom all but 8 inches of jejunum were resected successfully. In 1953, Julius J. Carucci[13] reported 3 successful resections.

This condition seems to have received recognition in the last decade. Upon questioning other physicians in Grand Forks, North Dakota, 2 additional cases were revealed in this community. From these accounts and the previously reported papers, the paucity of information relative to venous mesenteric thrombosis may be due to reluctance on the part of surgeons to (1) have postmortem examinations performed, and (2) to report cases with unhappy terminations.

CASE HISTORIES

Case 1. White female, age 25, was seen at her home June 4, 1927. She was writhing in pain of sudden onset, which she described as similar to menstrual cramps only 100 times worse. Her abdomen was soft and her temperature normal. She was given ¼ gr. of morphine sulfate and 1/150 gr. of atropine. Relief lasted only a short time. Hospitalization was advised.

Her past history contributed little. She had previously undergone salpingectomy, appendectomy in 1923, and cholecystectomy in 1925. On admission she had not vomited, her temperature was 97°, her abdomen was soft with no distention, no spasms had occurred, no masses were found, and bowel sound was present.

On June 5 lower abdominal pain was still severe and minimum muscle spasm occurred. On June 6 she vomited, her abdomen was distended, cul-de-sac boggy. June 7 colpotomy was done, and black foul fluid was released. June 8 and 9 her condition progressively became worse in spite of supportive treatment of that time. She expired on the fifth day. The severe pain without signs or symptoms to explain it was the outstanding feature of this case. The pathologic report at necropsy revealed (1) old varicose endocarditis, (2) chronic nephritis, (3) passive congestion of kidney, and (4) thrombosis of the superior mesenteric vein.

Case 2. The patient, a 38-year-old farmer's wife, gravida V and para IV was first seen November 28, 1953, with complaints relative to an enlarged, infected Bartholin cyst. The cyst was incised, drained, and the patient started on 800,000 units of penicillin G and sitz baths. She complained of mild epigastric distress and nausea three days later, which was believed due to morning sickness. She was given Emetrol, antacids, and antispasmodics and experienced immediate relief of symptoms.

On December 6 she was admitted to Northwood Deaconess Hospital and the following day under spinal anesthesia, 90 mg. of procaine, the Bartholin cyst was excised. The postoperative course was completely uncomplicated and the patient was discharged on the second postoperative day. She was awakened by severe abdominal pain and nausea seven hours after discharge. She re-entered the hospital the next morning, December 10, 1953, having had no relief in symptoms. Examination at that time revealed blood pressure 110/80, pulse 74, and respiration 18. Positive physical findings included only voluntary muscle spasm on palpation of the abdomen, especially in the left lower quadrant and midepigastrium. Bowel sounds were normal. Pelvic examination revealed only a uterus enlarged to two and one-half to three months' gestation. Laboratory studies indicated 22,750 leukocytes with a pronounced shift to the right; hemoglobin, 12.95 gm.; and 4,320,000 red blood cells. Urinalysis revealed 1.008 specific gravity, albumin was negative, and sugar was negative. Microscopic study showed 4 hyaline casts and 5 white blood cells to the low power field. Serum amylase drawn shortly after admission was 45 units, but was delayed due to the distance to the laboratory.

The patient was given ¼ gr. of morphine sulfate with little relief of symptoms. Atropine sulfate, 1/150 gr., offered only slight relief. The abdomen gradually became distended, pain was rhythmical and increased in character, and the pulse increased to 130. She was taken to the operating room for exploratory laparotomy twelve hours after admission.

Under general anesthesia the abdomen was prepared and draped. A right rectus incision was made. On opening the peritoneum, 2 to 3 liters of blood-tinged fluid exuded. A large segment of the ileum was seen to be gangrenous. This segment was brought into the wound. At points 2 inches proximal and distal to the involved area the bowel was clamped, cut, cauterized with phenol and alcohol, and the stumps closed with chromic suture. The gangrenous segment was resected and the mesentery suture ligated. A side-to-side anastomosis was then done. Examination of the pelvis showed no abnormality; the uterus was enlarged to three months' gestation. A rubber drain was placed in the intestinal bed. The abdomen was closed in layers.

Gross pathology. Specimen consisted of a portion of the small intestine with a part of the mesentery attached. The total length of this bowel was about 1 meter. At one end of this specimen the mucosa was gray to tan, appearing normal and measuring 6 cm. in length. At the opposite end the mucosa was similar and extended for about 2 cm. in length. This intestine was opened longitudinally on the antimesenteric side. The majority of the serosa and mucosa was tan to brown. Representative sections were submitted for microscopic study.

Microscopic pathology. Multiple sections through the intestine and through the mesentery showed moderate diffuse areas of hemorrhage with focal areas of leukocytic infiltration, particularly about some blood vessels. A number of the venules and some of the larger veins in the submucosa, serosa, and in the mesentery showed thrombosis.

Pathologic diagnosis. Early infarction gangrene of the small bowel and mesenteric venous thrombosis.

The patient withstood the procedure well. Levin suction was continued; intravenous fluids and antibiotics given throughout the postoperative course. Depo-Heparin in doses of 200 mg. was given daily. Ice chips were begun on the third postoperative day and a liquid diet on the sixth day. Cortisone was started on the thirteenth day and continued with gradual diminishing doses after discharge. A total of 6 units of whole blood was given. She was discharged three weeks after operation and a soft diet prescribed.

The patient was followed at bimonthly intervals throughout the remainder of her pregnancy. The only difficulty encountered was excessive weight gain of a total of 34 lb. over the six months' period, which was controlled by ammonium chloride periodically.

Labor began spontaneously at term. The patient was

started on cortisone as a precautionary measure at that time. Her labor lasted four hours and resulted in the spontaneous delivery of a female infant who cried immediately. The infant weighed 8 lb. 4½ oz. Postpartum course was uncomplicated. Cortisone was decreased stepwise after the second postpartum day. The infant was breast fed until the seventh day when she developed a generalized skin rash which responded well to a change in formula. At six weeks' check-up the infant weighed 10 lb. 4 oz. The mother had had no abdominal complaints and is now on a regular diet and has done all of her own work since six weeks after the second operation.

DISCUSSION

The most striking feature of this case was the extreme pain and the disproportionate lack of supporting physical findings on examination.

Remembering case 1, the similarity was striking. A luetic crisis or pancreatitis were the only other conditions that reasonably could produce the picture. Her marital history made lues improbale. A blood serum amylase ruled out pancreatitis. Exploratory laparotomy was elected. As it happened, perhaps the time we expended in obtaining the serum amylase was well used; as had we operated when she was first seen, probably sufficient time would not have elapsed for demarcation to develop. As it was, definite demarcation was evident, and we knew just how much bowel must be removed. The etiology at this point is rather obscure. It is interesting to speculate on a possible connection between surgery on the perineum or, more specifically, the Bartholin glands and a probable course of an embolism to the superior mesenteric veins, assuming this to be the cause of the thrombosis.

A review of the anatomy of the venous drainage of the perineum in Cunningham's anatomy book states that "The pelvic venous plexuses form dense networks of thin-walled veins associated with the rectum, bladder, prostate, uterus, and vagina. They communicate freely with one another, and from them the visceral tributaries of the internal iliac veins arise.

The rectal plexuses lie in the submucous coat of the rectum and anal canal and on the outer surface of their muscular coats. They are drained by the superior, middle, and inferior rectal veins; the superior rectal vein joins the portal system; there the inferior mesenteric joins the splenic vein which in turn joins the portal; the middle and inferior are tributaries of the systemic veins. The rectal plexuses, therefore, form a link between systemic and portal veins."

Is it logical to assume that the pressure of the enlarging uterus may have been a factor in changing the venous flow from the systemic system into the portal system and can an embolism be assumed to have broken loose to travel retrograde, due to higher venous pressure of the portal vein and so sow the seed for a thrombosis in the superior mesenteric vessels?

The lessons to be gained from this case seem to be that: (1) If possible, pelvic, perineal, and rectal surgery should be avoided during pregnancy. (2) If a patient has excruciating abdominal pain and if a definite diagnosis cannot be readily made, he should be treated as a surgical emergency and an exploratory laparotomy performed.

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A Firm Efficient Method of Repair for Old Injuries of the Perineum in the Female

DANIEL H. BESSESEN, M.D.
Olivia, Minnesota

FORTUNATELY many different operative technics for repair of defects in the posterior perineum of the female are available to the gynecologic surgeon. The operator is able to choose freely that method which best meets the peculiar needs of the individual patient.

This lesion may occur independently of other defects, but is most often seen in conjunction with a generally relaxed pelvis – one which requires a complete pelvic repair. Over the years one method of posterior perineorrhaphy above all others has seemed to me more appropriate.

If there are defects other than those relating to the pelvic floor, a prolapse of the rectum is the more common, or a bulbar anterior rectal pouch. Most helpful in improving the rectal condition is the surgical maneuver described in this article. It is not enough to secure a strong pelvic support, but the rectal dislocation must also be returned to normal with its normal function. In such cases, the resulting thickened perineal body with a shortened anteroposterior perineum achieves an almost certain correction of any rectal problems. This is especially true if combined with a shortening of the sacro-uterine ligaments which lifts the sigmoid-rectal junction.

DANIEL H. BESSESEN, *a 1922 graduate of the University of Minnesota, is a surgeon at the Renville County Hospital, Olivia, Minnesota.*

The usual inverted V-shaped dissection of the posterior vaginal mucosa is made, beginning at the mucocutaneous margin (figure 1). This must be continued well up into the vault of the vagina. At either side the thickness of the levator ani muscles can be felt beneath the submucosal soft tissues. A curved scissors is thrust through this fascial layer which covers the levator ani muscles. By extending this opening through the fascia or scar tissues, 3 layers of tissue must be united in the midline: superiorly, fascia; in the middle, muscle; and inferiorly, fascia.

Uniting these 3 layers each individually in the midline by means of a figure 8 stitch (figure 2) not only brings them together medially but reduces the distance from the anus to the vagina, shortening the perineum and making still more firm the support of the pelvic floor. Uniting each layer separately – fascia, muscle, fascia – allows for a greater flexibility than would be the case if deep sutures were planted through the fascia and muscle combined (figure 3).

Closing the soft tissues and the mucous membrane and skin, completes the operation (figures 4 and 5). The final inspection of the rectal mucosa is routine. This type of rectocele repair gives a perineum as strong as that in the virgin. It is the method of choice where other factors do not contraindicate its use and is a simple but sure repair.

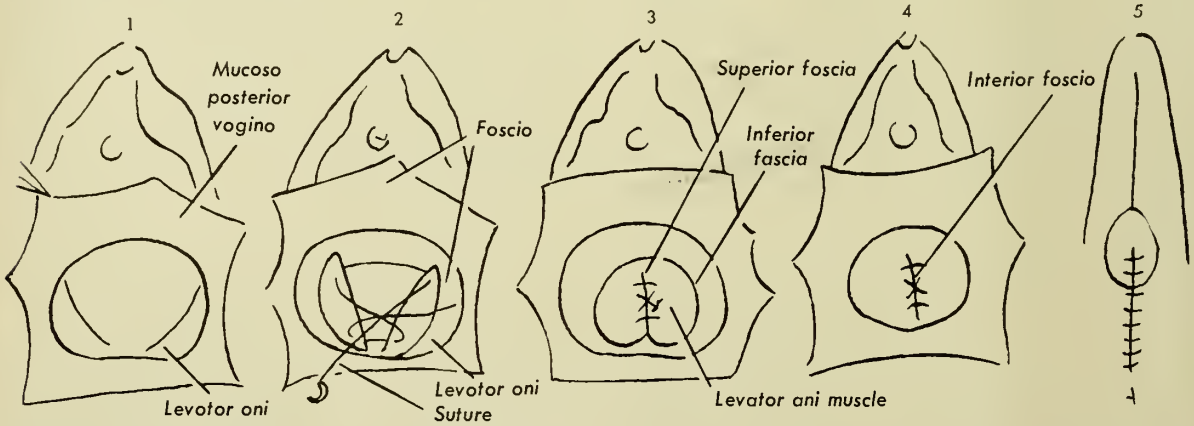

Fig. 1. Dissection of mucosal layer from posterior vagina. Levator ani muscles are revealed in the lower corners of the dissection. Fig. 2. Incision into overlying fascia with muscle fibers in the aperture. Figure 8 stitch is placed. This same suture is inserted into the muscle fibers and then again into the inferior layer of fascia. Fig. 3. Suture is tied in superior fascia. Muscle fibers are shown in levator ani with the inferior layer of fascia, both of which are sutured in manner similar to superior fascia. Fig. 4. Suture placed and tied in inferior fascia. Fig. 5. Final skin suture in place. Drawing shows shortened anteroposterior perineum.

A Clinical and Experimental Study of Agammaglobulinemia

ROBERT A. GOOD, M.D., and RICHARD L. VARCO, M.D.
Minneapolis, Minnesota

Agammaglobulinemia and extreme hypogammaglobulinemia occur as concomitants of several human diseases. Depression of the serum gamma globulin concentration may occur because of loss of protein from the body, generalized failure of protein fabrication, inordinately rapid destruction of serum protein, or because of an isolated deficit in gamma globulin synthesis.

In the nephrotic syndrome, for example, hypogammaglobulinemia and hypoalbuminemia occur reflecting the loss of these two protein components in the urine.[1] Patients with nephrosis are not lacking in capacity to synthesize protein. Instead, Kelley and associates[2] showed that increased rather than decreased protein fabrication characterizes patients with this disease. These findings are in substantial agreement with the conclusions of Kunkel and Ward[3] and others,[4] that patients with nephrosis are producing more than normal amounts of serum albumin in an attempt to keep up with the urinary losses. That the same conclusions hold for the gamma globulin metabolism in these patients has recently received experimental support.

Hypogammaglobulinemia and perhaps even agammaglobulinemia occur also as part of a disease featured by failure of protein production originally observed by McQuarrie and associates.[5-7] Similar patients have since been studied and reported by others.[8-10] In the original patient studied by McQuarrie, the patient's disease was featured by generalized edema, very low total serum proteins, especially low serum globulins, and inordinate susceptibility to infection. Fried and Henley[11] studied a similar case and emphasized the deficiency of circulating gamma globulin in these patients. In this disorder, the albumin and globulin deficiency was attributed to failure of fabrication of serum proteins by the liver. Occasionally, as pointed out by Krebs,[12] nutritional deficiency may result in hypogammaglobulinemia associated with generalized hypoproteinemia. Hypogammaglobulinemia along with generalized hypoproteinemia may also be a function of excessively rapid destruction or utilization of serum protein as in a patient intensively studied by Dixon.[13] Recently Ulstrom and associates[14] described an infant suffering from hypoproteinemia, edema, anemia, and agammaglobulinemia in whom all the abnormalities were self limited.

In each of the above disorders of protein metabolism, depression of gamma globulin concentration occurs in the plasma or serum, but in each instance it is associated with a disturbance in the metabolism of other serum protein components.

In 1952, Bruton,[15] and Bruton and associates[16] described a disease entity expressed clinically as an inordinate susceptibility to bacterial infection. Electrophoretic studies revealed that this disease was featured by complete absence of gamma globulin from the serum. Bruton's patient, an 11-year-old boy, was shown to be lacking in circulating antibodies and to be unable to produce antibodies in response to antigenic stimulation. Unlike the instances of agammaglobulinemia previously described, electrophoretic analysis of the plasma or serum from this patient revealed a protein partition essentially normal except for the absence of gamma globulin. Following Bruton's case report, Janeway and Gitlin[17] gathered together 9 such cases. Each of the latter group exhibited the cardinal features described by Bruton, namely: (1) increased susceptibility to bacterial disease, (2) absence of gamma globulin in the serum, (3) absence of antibody in the blood and tissues, and (4) failure of antibody production in response to antigenic stimulation.

These studies of the Boston group established that agammaglobulinemia is due to failure of synthesis of this particular electrophoretic component of the serum proteins and is not a function of generalized protein dysmetabolism. Further, it was established that this type of agammaglobulinemia is not due to inordinately rapid decay of gamma globulin. For example, parenterally administered gamma globulin had, in these patients, a half life essentially the same or somewhat longer than that described by others[18-20] for normal human subjects. During the

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

past two years, electrophoretic analysis of the serum of patients showing increased susceptibility to bacterial infection has turned up many instances of agammaglobulinemia.[21-28] Almost every laboratory in a medical center having both a large patient load and an electrophoresis apparatus has turned up at least 1 such case. Patients with this disease develop severe illnesses regularly. Their susceptibility to infection is undoubtedly a function of the lack of gamma globulin and lack of ability to form antibodies—one of the established mechanisms of defense against infection. Present data suggest there exist at least 2 clinical forms of isolated agammaglobulinemia.

The form of the disease described by Bruton seems to be a congenital disease. It has further been suggested by Janeway and Gitlin[17] that this illness is a function of an inborn error of metabolism which is transmitted as a sex-linked recessive trait. This concept derives support from the observation that all of the patients with the congenital form of the disease thus far described have been boys, that in several instances more than 1 male child of a sibship has had the disease, and that historically there is the suggestion that maternal uncles or male offspring of a maternal aunt have died of severe infections in infancy and presumably have had agammaglobulinemia. This type of anomaly of protein synthesis has its prototype in hemophilia. The latter disease too is an inborn error of protein formation resulting in the absence of a particular globulin component from the blood. As with agammaglobulinemia, hemophilia is an hereditary protein deficiency transmitted as a sex-linked recessive factor. Somewhat similarly, with respect to fibrinogen,[29,30] a hereditary hemorrhagic diathesis has been discovered which is due to the complete absence of a particular protein component, namely fibrinogen, from the circulating blood. The latter syndrome, referred to as afibrinogenemia, has been intensely investigated by Macfarlane[31] and by Frick and McQuarrie.[32] Somewhat differently afibrinogenemia seems to be inherited as a simple Mendelian recessive trait, is often a function of a consanguinous marriage, and is a disease in which the heterozygous recessive trait may be expressed as hypofibrinogenemia.

The form of agammaglobulinemia occurring in male children, then, is sex-linked, congenital, and familial. Whether congenital agammaglobulinemia requires further subdivision into pronounced hypogammaglobulinemia and complete agammaglobulinemia, or, more precisely, into a form of the disease featured by complete generalized "immunologic paralysis" and a form featured by less complete immunologic handicap must be decided on the basis of future study. The latter possibility is suggested by our observations which follow.

In addition to and distinct from this group of patients, agammaglobulinemia has been found to occur in adults. As in the childhood disease, agammaglobulinemia in adults is expressed clinically as a pronounced decrease in resistance to bacterial infection. The latter form of agammaglobulinemia appears to begin at any age in either sex and clinical evidence indicates that it is an acquired disease. Preliminary studies indeed suggest that delicate quantitative immunologic methods further separate congenital agammaglobulinemia and acquired agammaglobulinemia from each other on the basis of the gamma globulin concentration as measured in this way. In the congenital disturbance, the agammaglobulinemia may be complete or the serum may contain only minute amounts of gamma globulin, whereas in the adult disease somewhat higher concentrations of gamma globulin are present in the serum. Support for this classification derived in a different way will be presented in this report. Electrophoretically, however, using both the paper technic and free electrophoresis, both diseases are expressed as an absence of detectable gamma globulin in the serum or plasma.

During the past ten months we have discovered and studied 8 patients with agammaglobulinemia revealed electrophoretically as an isolated disturbance of protein synthesis. Of these patients, 6 are children representing 4 families, and 2 are adults. The children are all boys. One adult is female and the other male. Each of the patients suffered from an illness featured by recurrent severe bacterial infections. Both of the adults and 3 of the children have been subjected to intensive clinical, hematologic, pathologic, and immunologic investigation in an attempt to elucidate the nature of the handicap, to define in these patients the relationship of the congenital to the acquired disease and to make inquiry into a number of fundamental immunologic problems to which an incisive approach is offered by this revealing experiment of nature.

CASE HISTORIES

Congenital agammaglobulinemia.

Case 1. E. S. is a 7-year-old boy born in Germany of Latvian parents who are unrelated. This child was well until he was 7 months of age. At that time he developed severe diarrhea complicated by pneumonia. He was treated with sulfadiazine and seemed to recover completely. However, during the first four years of life, he suffered repeated episodes of respiratory infection with high fever,

otitis media, and pneumonia. He responded well to chemotherapy and antibiotic therapy but was in almost constant trouble with the recurrent episodes of bacterial disease. During the next three years, this boy suffered from bacterial meningitis on 3 occasions, bacterial pneumonia 3 times, severe life-threatening laryngotracheobronchitis, septicemia twice, bacterial infection of the urinary tract, and numerous episodes of bacterial infection of the respiratory tract usually with frank otitis media. For several weeks during 1953, when he was free of overt infection, the observation was made that he possessed low levels of neutrophils. This hematologic abnormality persisted for approximately one month. In a number of instances the etiologic agent responsible for the infections was specifically identified. The pneumococcus caused 2 episodes of meningitis, and 1 was due to *Hemophilus influenzae*, group B. Several episodes of pneumonia were attributed to pneumococci and 1 urinary infection was caused by a proteus. In every instance, the infections responded well to antibiotic therapy. There was no doubt in the minds of the responsible physicians that antibiotic therapy had been lifesaving many times. In spite of all these infections, this 7-year-old boy is a large, well-developed, well-nourished lad with little residual evidence of his many infections. Attempts to vaccinate this patient against smallpox were carried out 3 times and no reaction whatever was produced. He was given diphtheria toxoid several times but remained Schick negative. Upon admission to the University of Minnesota hospitals, an electrophoretic pattern of the serum proteins was performed and a diagnosis of agammaglobulinemia was made. The diagnosis of agammaglobulinemia was based on absence of the gamma fraction on both paper and free electrophoretic patterns of plasma and serum. It was noted on laboratory examination that he possessed no isoagglutinins versus heterologous blood group substances and that the zinc turbidity reaction was zero.

Case 2. W. A., a 6-year-old white male, born after a normal gestational period terminated by a normal delivery was troubled, between 3 and 6 months of age, with skin disease which was thought to be infected eczema. He developed meningitis at 9 months of age which responded to treatment with penicillin and sulfadiazine. When 13 months old, he developed peritonitis, abdominal abscess, and septicemia which responded after a prolonged period of broad spectrum, intensive antibiotic therapy and chemotherapy. At 18 months of age, he underwent an interval appendectomy but no evidence of previous appendicitis was found. During the next three years, he had at least 7 attacks of pneumonia and repeated attacks of otitis media and mastoiditis. On several occasions, during the course of the infections, it was noted that the granulocyte count was very low, and a diagnosis of agranulocytosis was entertained. However, the granulopenia proved to be transient in each instance.

In January 1953, the patient had a febrile illness with headache followed by severe paralysis of both legs. A diagnosis of Guillain-Barré syndrome was made in retrospect, but the history and residual manifestations are strongly suggestive that this disease was poliomyelitis. During 1953, he suffered recurrent respiratory disease and several episodes of pneumonia. Finally it was found that bronchiectasis was present and a lobectomy was performed. In spite of the surgical procedure, pulmonary infections continued to occur, and bacterial pneumonia developed on several additional occasions. Finally, in July 1954, he was admitted to the University of Minnesota hospitals for study and treatment. Laboratory studies revealed the complete absence of gamma globulin on both free and paper electrophoretic analysis of the serum proteins. X-ray studies, including bronchograms, revealed bronchiectasis in the remaining portions of the right lung. Bronchograms of the left lung were normal.

Case 3. T. A., an 8-month-old male sibling of case number 2, was discovered to have agammaglobulinemia at the age of 2 months during a laboratory survey of the entire family for evidence of this disease. Up to the present time, this child has had no infections save 2 nonbacterial upper respiratory infections which were not unusual in any respect. At the age of 4 months, he spontaneously developed a profound granulopenia lasting two months. The granulopenia disappeared spontaneously. Diagnosis was made by both paper and free electrophoretic analysis of the plasma and serum proteins and was further indicated by absence of isoagglutinins versus heterologous blood group substances and a negative zinc turbidity reaction.

Case 4. F. T., a 20-month-old male child, was well until 7 months of age when he developed pneumonia with high fever and profound collapse. Although it was noted that his white blood count was abnormal and was featured by neutropenia, he responded well to antibiotic therapy. He had no more than recovered when he contracted pneumonia a second time. Again antibiotic treatment resulted in recovery. He was recurrently and severely ill with otitis media, pneumonia, and septicemia. On each occasion, response to antibiotic therapy was achieved in spite of the abnormally low numbers of neutrophils in the peripheral blood. He was admitted to the University of Minnesota hospitals in 1952 and studied over a four-month period. During this study, a diagnosis of cyclic neutropenia was made. Although serum was saved in the frozen state as part of a banking procedure in connection with another study, electrophoretic analysis of the serum proteins was not performed until after his death. The child experienced recurrent attacks of pneumonia, about 10 in all, associated with septicemia on several occasions. Otitis media likewise occurred several times. In each instance, the bacterial infections due to streptococci, pneumococci, Pseudomonas, and proteus organisms responded quite well to specific antibiotic therapy. After four months of hospitalization, during which the child demonstrated a cyclic neutropenia featured by a 20 to 22 day cycle, the patient developed pneumonia, extreme neutropenia, and stiffness of the neck and back. In this final illness, cultures of throat and sputum revealed gram-negative organisms and staphylococci. Blood cultures were negative; spinal tap revealed the presence of a high protein content—90 mg. per cent—and moderate lymphocytic exudate, but grew no organisms. The child became comatose, developed intractable vomiting, and expired on January 1, 1953 in spite of most intensive, broadly empiric antibiotic therapy. A complete postmortem examination was performed which revealed that extensive interstitial pneumonia was the probable cause of death. The etiologic agent responsible for the pneumonia was not determined. In retrospect, analysis of the stored serum revealed the presence of agammaglobulinemia on both paper and free electrophoretic patterns. The zinc turbidity test of Kunkel gave an insignificant reaction, and isoagglutinins against heterologous blood group substances were present in very low concentration. This patient was successfully vaccinated at 6 months of age and recovered from measles at 14 months without event.

Case 5. T. T., a 15-month-old sibling of case number 4, also died before a diagnosis of agammaglobulinemia was made. Like his brother, this boy was well until he was 6 months old. At 6 months of age, he developed measles which was expressed with the usual symptomatology and from which he recovered spontaneously without event. Between the ages of 7 and 8 months, he had diarrhea associated with high fever. Sulfadiazine treatment of this infection was successful. At 8 months of age he developed pneumonia and a severe neutropenia was discovered. Treatment with penicillin resulted in clinical recovery, but the neutropenia persisted. He was admitted to the University of Minnesota hospitals after an attack of varicella, the course of which was uneventful. The reason for admission was that he developed an infection of the thumb followed by staphylococcus septicemia. This infection responded well to treatment with Aureomycin. Because the neutrophil count was persistently low, because his older sibling with the same clinical illness had died as a consequence of his disease, and because Fullerton and Duguid[33] suggested that clinical and laboratory improvement in cyclic neutropenia may follow removal of the spleen, splenectomy was performed June 19, 1953. Convalescence was complicated by the occurrence of a staphylococcal abscess of the thigh and bacteremia. Treatment with several antibiotics eradicated this infection. During the subsequent two weeks, the neutrophil count rose to the normal range. However, within a month the level dropped to the low levels present prior to splenectomy, where it persisted until his death ten months later. Although, for a short period after splenectomy, he was kept free of infections by the use of prophylactic antibiotic therapy, he again developed trouble with recurrent otitis media, generalized respiratory disease, and pneumonia. He finally developed respiratory and urinary tract infection and then septicemia with staphylococci and proteus organisms resistant to all available antibiotics. He succumbed after the occurrence of vesical-enteric fistula. Postmortem examination was not permitted.

In neither of the latter 2 cases was the diagnosis of agammaglobulinemia suspected during life. The extreme susceptibility to infection seemed to be well explained by the deficit of neutrophils. However, as part of a study of acute-phase serologic reactions in childhood, blood samples were taken and serum saved in the frozen state at -26°C. When it was discovered that persistent neutropenia developed without infection in a proved case (case 3) of agammaglobulinemia and that each of 2 other patients with well established disease (cases 1 and 2) showed episodic neutropenia in the apparent absence of infection, stored blood samples from these 2 children were studied. The result was the demonstration of agammaglobulinemia by both paper and free electrophoretic technics in each instance.

Case 6. J. S. was a 7-month-old male child, born by normal labor and delivery. He did well until 3 months of age when he developed pneumonia. Recovery occurred with antibiotic therapy, and he was well until 5 months of age when he developed pneumonia again. A third severe respiratory infection diagnosed as pneumonia occurred at 6 months of age. The family history was of interest in that several members of the family were troubled with asthma, eczema, or hay fever. The child was a large healthy infant having no physical abnormalities. Routine laboratory workup was negative. The zinc turbidity reaction was zero; the baby was blood group O and possessed no antibody against heterologous blood groups. Both free and paper electrophoretic patterns showed complete absence of gamma globulin. (We are indebted to Dr. T. C. Papermaster for discovery of this patient.)

Acquired agammaglobulinemia.

Case 7. F. H. is a 58-year-old male who was well until four years prior to admission when he developed pneumonia for the first time. He had recurrent respiratory symptoms and chest roentgenogram revealed evidence of a large thymoma. Exploration for the thymus tumor was delayed several months because of recurrent respiratory infection including another episode of pneumonia. The respiratory disease responded to treatment with sulfadiazine and penicillin. On November 6, 1951, a 540-gm. tumor was removed from the anterior mediastinum. On microscopic examination, it was concluded that this tumor represented benign thymoma and consisted primarily of proliferation of thymocytes and thymic reticulum cells. A serum protein determination performed on November 6, 1951, just prior to the operation, revealed a low total serum protein concentration of 5.4 mg. per cent. Protein fractionation was not performed.

During the past four years, F. H. has had 17 attacks of pneumonia. Because the attacks occurred with greater and greater frequency, he was admitted to the University hospitals for study. Laboratory studies revealed evidence of diffuse pneumonia with the usual concomitant, laboratory, and clinical manifestations. Treatment with antibiotics was already begun and so no pathogens were isolated from the sputum. Electrophoretic analysis of the serum proteins revealed absence of gamma globulin from the serum. In the course of the clinical workup, it was discovered that this patient possessed no circulating eosinophils and that the eosinophilic development in the bone marrow was lacking.

Case 8. L. L., a 30-year-old white female was well until eight years ago when she began to be troubled with recurring bacterial disease. During this period she has had 3 attacks of pneumococcal meningitis, at least 34 attacks of pneumonia, which several times were lobar in character and proved on a number of occasions to be due to pneumococci, numerous attacks of otitis media, and almost constant paranasal sinusitis. Beginning over three years prior to study, she developed lymphadenopathy, splenomegaly, and hepatomegaly due apparently to an ill defined disorder of the fixed and free reticulum. The pathologic features of the latter disease include granulomata throughout the reticular tissues and diffuse reticular hyperplasia. A resemblance of the granulomatous process to sarcoid has been mentioned, but the latter diagnosis is not acceptable to most of the pathologists who have studied the material. Three years prior to study, she developed a Coombs' test-negative hemolytic anemia which responded dramatically to splenectomy and has been attributed to hypersplenism. The diagnosis of agammaglobulinemia was made by the observation that gamma globulin was absent on both free and paper electrophoretic analyses of the serum and plasma. The patient is blood group A, isoagglutinins are absent and the zinc turbidity reaction was zero. (This case was recently reported in extenso by Prasad and associates.[23])

Table I summarizes the results of the serum protein analysis performed in these patients according to standard methods. Fractionation of the albumin and globulin was performed with 26 per cent sodium sulfate. The zinc turbidity determination was performed according to the

TABLE 1
SERUM PROTEINS IN AGAMMAGLOBULINEMIA

Patient	Age	Total protein	Albumin	Globulin	A-G ratio	Zinc turbidity
E.S.	7 yr.	5.7	4.2	1.5	2.80	0 units
W.A.	7 yr.	5.5	3.5	2.0	1.75	0 units
T.A.	6 mo.	5.5	4.0	1.5	2.66	0 units
F.T.	20 mo.	5.5	2.5	3.0	0.83	1 unit
T.T.	15 mo.	5.7	3.2	2.5	1.28	2 units
F.H.	58 yr.	5.4	3.5	1.9	1.84	0 units
L.L.	26 yr.	6.2	4.6	1.6	2.87	0 units

TABLE 2
ELECTROPHORETIC ANALYSIS OF THE SERUM PROTEINS IN PATIENTS WITH AGAMMAGLOBULINEMIA

	Protein Fraction gm. per cent					
Patient	Albumin	Alpha 1 globulin	Alpha 2 globulin	Beta globulin	Gamma globulin	Total serum preotein
E.S.	4.20	0.29	0.69	0.82	0.00	6.0
W.A.	3.68	0.65	0.38	0.78	0.00	5.5
T.A.	4.55	0.38	0.23	0.33	0.00	5.5
F.H.	2.85	0.72	0.99	0.84	0.00	5.4
L.L.	3.86	0.66	0.76	0.92	0.00	6.2
F.T.	3.44	0.96	0.79	0.27	0.03	5.5
T.T.	2.99	1.19	1.19	1.02	0.00	5.7

method of Kunkel.[34] As may be seen in the table, the total protein concentration in these patients was uniformly low or at the lower limits of normal. The albumin concentration was, however, regularly within the normal range and the slight depression of total serum protein observed was attributable to a deficiency of circulating globulin. The result of this protein distribution was in almost every instance an increased albumin-globulin ratio. Such a protein fractionation in our experience is a distinctly unusual finding in patients presenting, as these patients did, a history of chronic or recurrent infection. The zinc turbidity test performed many times in these patients showed either no turbidity or an insignificant reaction, 0 to 1 unit. Normal values for gamma globulin precipitated with zinc sulfate according to Kunkel's technic is 5 to 6 turbidity units in children and the range is from 2 to 13 units. Electrophoretic analysis of the serum proteins (table 2) in most of the patients revealed essentially normal values for each of the components save gamma globulin. Just as in normal persons, however, during severe infections, elevations of alpha globulin were noted in several instances. On electrophoretic analysis the gamma fraction was completely absent in each case. It is on the basis of the electrophoretic patterns from each patient (figure 1) that the diagnosis of agammaglobulinemia was made.

Table 3 summarizes results of complete liver function tests performed in 5 of the 7 patients. No significant deviation from normal values was found with the exception of the low concentration of globulin and the decreased zinc turbidity reaction. Even the most delicate indices of hepatic adequacy, the bromsulphalein retention test and the twenty-four-hour urine urobilinogen excretion fell within normal limits. Another observation, to be reported in detail elsewhere,[35] was that liver biopsy on 1 of the adults and postmortem examination of the liver in 1 of the children revealed no abnormalities in the morphology, organization, or tinctorial properties of the hepatic parenchyma. These observations, indicating an intact morphology and physiologic function of the liver, must be interpreted as support for the concept that isolated failure of gamma globulin synthesis is not attributable to generalized hepatic malfunction. As corollary to this conclusion must also be the consideration of the strong likelihood that gamma globulin and antibody formation occur at an extrahepatic site.

A detailed study of the coagulation mechanism was carried out in 4 of these patients. This was done in an effort to exclude the concomitant occurrence of a deficiency of proteins other than gamma globulin which might be reflected as an anomaly of coagulation. Table 4 summarizes the results of this study. No abnormalities were observed in the Lee White clotting time, Ivy bleeding time, 1-stage prothrombin time, 2-stage prothrombin time, recalcification time,

TABLE 3
STUDIES OF LIVER FUNCTION IN PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	Serum bilirubin 1' mg.%	Serum bilirubin total mg. %	C.C. 0-4+	T.T. unit	Cholesterol mg. %	Cholesterol esters mg. %	U.U. mg./d	Cholinesterase △ph/hr.	B.S.P. % retention
E.S.	0.1	0.4	0	0	108	70	0.8	0.74	1%
T.A.	0.3	0.4	0	1	77	57	trace	0.81	1%
W.A.	0.1	0.3	0	0	175	122	0.4	0.45	1%
F.H.	0.1	0.4	0	0	212	160	0.3	0.61	0%
L.L.	0.1	0.4	0	0	252	189	0.4	0.86	0%

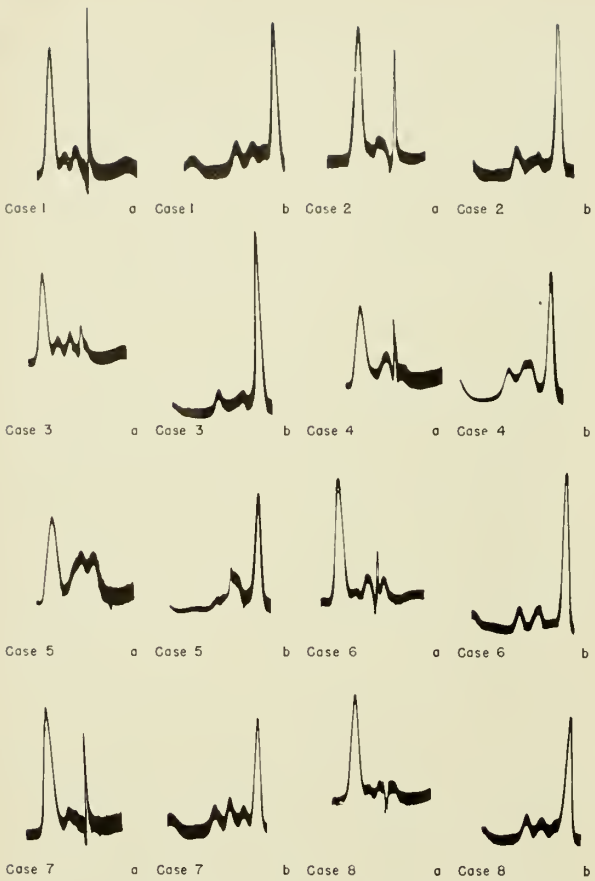

Fig. 1. Electrophoretic analyses of patients with agammaglobulinemia.

thrombin titration, platelet count, clot retraction, Rumpel Leede test, or the prothrombin consumption. The observation of normal values for each of the systematically arranged coagulation tests[36] supports the concept formulated on the basis of data obtained by electrophoretic and chemical fractionation of serum proteins that in this disease a deficiency exists in the synthesis of only one protein component, namely, the gamma globulin fraction. Since evidence has been presented indicating that many of the protein factors involved in the clotting mechanism are actually produced in the liver and are decreased in concentration in the course of severe liver disease, the finding of entirely normal clotting mechanism in agammaglobulinemic patients supports the contention that liver function, particularly concerning protein synthesis, is normal in these patients and that failure of gamma globulin synthesis occurs in the face of hepatic integrity. Further, this study provides substantial evidence that none of the factors involved in clotting of blood is a gamma globulin.

Summarizing to this point, we are reporting 6 children suffering from the congenital form of agammmaglobulinemia and 2 adults having the acquired form of this disease. In each instance, the syndrome presented itself as an extreme susceptibility to bacterial infection, beginning in the children during the second half of the first year of life, probably after loss of passively transferred maternal gamma globulin. The value of the clinical history in establishing the diagnosis of agammaglobulinemia is attested by the fact that in the 2 latest cases studied, the diagnosis offered by the admitting house officer was agammaglobulinemia.

Routine laboratory studies may reflect the presence of infection or may reveal an underlying leukocytic disturbance. In several instances, the routine workup was entirely negative. Studies of the serum proteins by standard methods revealed an abnormally low total protein concentration, normal albumin, low globulin, and consequently an increased A-G ratio. The zinc turbidity test was found to be a good screening test for this disease since the values obtained were abnormally low. For this reason, screening

TABLE 4
TESTS OF HEMOSTATIC MECHANISM IN PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Lee White clotting time*	*Ivy bleeding time*	*Prothrombin time 1 stage*	*Prothrombin time 2 stage*	*Recalcification time*	*Thrombin titration*	*Clot retraction*	*Platelet*	*Cuff test*	*Prothrombin consumption*
E.S.	I.13′30″ II.16′30″ III.19′50″	2′00″	Patient 12.4 Control 12.0	Normal	Normal	Normal	Normal	390,000	Neg.	Normal
F.H.	I.14′00″ II.17′00″ III.30′00″	3′30″	Patient 12.4 Control 14.6	Normal	Normal	Normal	Normal	256,000	Neg.	Normal
W.A.	I.15′30″ II.18′00″ III.20′30″	3′00″	Patient 12.8 Control	Normal	Normal	Normal	Normal	541,000	Neg.	Normal
T.A.	I.15′00″ II.19′30″ III.23′00″	2′30″	—	Normal	Normal	Normal	Normal	594,000	Neg.	Normal
Normal	Up to 30′	Up to 5′	No greater than 15″	Prothrombin 300 u/cc. (15″)	Below 3 minutes	Comparison to control only	—	150,000 to 500,000	—	90% consumption at end of 1 hour

tests using the zinc turbidity reaction can now be considered to permit a presumptive laboratory diagnosis of agammaglobulinemia. This latter finding is the more remarkable clinically since patients suffering, as these patients do, from recurrent or chronic infections usually show a clearly elevated zinc turbidity reaction.

Preliminary consideration of the data presented in the case histories suggests that agammaglobulinemia often coexists with profound hematologic disease. Whether the apparent cyclic neutropenia, persistent neutropenia, transient neutropenia, eosinopenia, extreme leukocytosis, thymic tumor, lymphadenopathy, splenomegaly, mentioned in the case reports are independent phenomena, hematologic disturbances secondary to infection, or are intimately linked to the basis for the agammaglobulinemia cannot be ascertained. Suffice the recognition for the moment that extreme anomalies of hematologic function do occur in association with agammaglobulinemia in both children and adults and detailed analysis of the hematopoietic organs becomes imperative in a thorough investigation of this syndrome.

DEMONSTRATION OF THE IMMUNOLOGIC HANDICAP

In an attempt to determine whether the agammaglobulinemia observed in these patients was associated with failure of the immune mechanism, a 6-phase study was conducted. This investigation included the following parts:

1. A search was carried out for evidence of antibody formation to antigens known commonly to stimulate normal persons.

2. Attempt was made to induce antibody production by stimulation with potent bacterial antigens.

3. Study of the so-called natural antibodies was made. This consisted of measurement of the capacity of the serum of these patients to agglutinate heterologous blood group cells, and comparison of this capacity to that of normal children.

4. Attempt was made to stimulate formation of isoagglutinins versus heterologous blood group substances by parenteral injection of "mismatched" cells.

5. Measurement of the antibody response of these patients to a variety of potent virus antigens was performed. The response obtained was compared to that of normal persons.

6. A study of the skin reactivity of patients with agammaglobulinemia to tuberculin, pneumococcal products, and streptococcal products was conducted.

The observations appear to establish the fact that all of the patients with agammaglobulinemia suffer a profound immunologic handicap. It has been shown that 3 of the children and 1 of the adults with agammaglobulinemia have been suffering from "immunologic paralysis." This statement is supported by the observation that no evidence whatever of responsiveness to antigenic stimuli was obtained. The other adult and 2 of the children, F. T. and T. T., must be classified, on the basis of present data, as having a profound "immunologic paresis." In the adult, F. H., a 58-year-old male, who has been studied thoroughly, the only evidence of antibody formation discovered was the occurrence in his serum of a low titer of antibody against the heterologous blood group cells. In addition, questionable increase in titer occurred on stimulation with group A cells. Finally, of 3 agammaglobulinemic patients stimulated with polio virus, only this same individual, F. H., produced demonstrable antibody titer and in this case the response was an extremely low, almost negligible response. The situation with F. T. and T. T. cannot be evaluated clearly, since their disease was diagnosed in retrospect after the death of both children and studies of immunologic responsiveness were not performed. However, the fact that an initial blood sample showed a significant isoagglutinin titer in each of these 2 children suggests that some immunologic responsiveness was present in these

TABLE 5

IMMUNOLOGIC STUDIES IN PATIENTS WITH AGAMMAGLOBULINEMIA

Immunologic determinations	*Patient*						
	E.S.	*L.L.*	*W.A.*	*T.A.*	*F.H.*	*F.T.*	*T.T.*
Schick test	+	+	+	−*	+	+	+
Dick test	+	+	+	−*	+	X	X
ASO titer	0	0	0	0	0	0	0
Streptococcal antihyaluronidase	0	0	0	0	0	0	0
Streptococcal antidesoxyribose-nuclease	0	0	0	X	0	X	X
Heterophile antibody	0	0	0	0	0	0	0
Cold agglutinins	0	0	0	0	0	0	0
Febrile agglutinins†	0	0	0	0	0	0	0
Mumps C.F.	0	0	0	0	0	0	0
Herpes neutralizations	0	0	0	0	0	0	0
Polio neutralizations	0	–	0	0	0	–	–

*At 3 months of age—negative results attributed to passively transferred maternal antibody. At 7 months of age, after extensive immunization with DPT antigen, this Shick test was positive.
X-not done.
†Typhoid H, O, and paratyphoid B, Proteus OX_2, OX_{19}, Brucella, Tularemia.

representatives of the congenital syndrome. The data supporting these conclusions with respect to immunologic responsiveness in patients with agammaglobulinemia follow.

Table 5 summarizes results of a survey conducted to find evidence of antibody formation by observation of skin or serologic reactivity to antigens commonly providing stimulation in the environment of normal persons. Each of the agammaglobulinemic patients, with the exception of the baby tested at 4 months of age, reacted positively to skin testing with Schick and Dick toxins indicating an absence of tissue antibodies against these ubiquitous antigens. The negative Schick and Dick reaction in this infant was attributed to antibodies passively transferred to the baby from his Schick and Dick negative mother. This contention is supported by the observation that at 6 and 8 months of age when the baby was retested, a positive reaction to both Schick and Dick toxins was observed. Further, none of the patients tested possessed significant amounts of antibody against streptolysin, streptococcal hyaluronidase, or streptococcal desoxyribonuclease. Almost everyone has had at least one streptococcal infection by the time he has reached his seventh year[37] and, as a consequence, almost everyone possesses detectable antibodies against at least one of these streptococcal antigens. That this is not so with the agammaglobulinemic patients is a reflection of their immunologic handicap. In addition, Forsman antibodies, cold agglutinins, and complement-fixing and virus-neutralizing antibodies, commonly found in the serum of normal patients, were lacking in these individuals. Further, isoagglutinins against heterologous blood group cells were completely lacking in 4 of the patients and very low titers were observed in the other 3.

Our interpretation of these data is that they establish the existence of an immunologic handicap in each of the individuals having electrophoretic agammaglobulinemia, while studies which follow serve as presumptive evidence of an immunologic paralysis in 4 of them. From these data, it must be concluded that the other 3 patients in our series probably suffer only an "immunologic paresis."

Table 6 summarizes the results of attempts to provoke an antibody response in 5 patients with agammaglobulinemia by the injection of potent bacterial antigens. Each patient was given, at different times, a course of immunizations against typhoid and paratyphoid organisms, pneumococcal polysaccharide, and commercial DPT vaccine. At suitable intervals, after antigenic stimu-

TABLE 6
RESPONSE OF AGAMMAGLOBULINEMIC PATIENTS TO STIMULATION WITH BACTERIAL ANTIGENS

Patient	*Stimulation provided*	*Evidence of antibody formation*	
		Before stimulation	*After stimulation*
E.S. 7-year-old male	Diphtheria—6 injections 0.5 cc. DPT over 4 month period	Schick positive	Schick positive
	2,000 million typhoid org., 1,000 million paratyphoid org. i.d., subcut. and i.v. over 3-week period	no titer H, O, or B agglutinins	no titer H, O, or B agglutinins
	Pneumococcal polysaccharide 0.08 mg. Type I and Type II antigens	no titer no precipitate 0 mg. antibody N.	no titer no precipitate 0 mg. antibody N.
F.H. 58-year-old male	Diphtheria—4 injections with 0.5 cc. DPT over 4 month period	Schick positive	Schick positive
	2,000 million typhoid org., 1,000 million paratyphoid org. subcut., i.d. and i.v. over 2-month period	no titer H, O, or B agglutinins	no titer H, O, or B agglutinins
	Pneumococcal polysaccharide 0.08 mg. Types I and II antigens	no titer 0 mg. antibody N.; no ppt.	no titer 0 mg. antibody N.; no ppt.
L.L. 26-year-old female	Diphtheria—3 injections with 0.5 cc. DPT antigen over 2 month period	Schick positive	Schick positive
	2,000 million typhoid, 1,000 million paratyphoid i.d., subcut. and i.v. over 2-month period	no titer vs. H, O, or B agglutinins	no titer, H, O, or B agglutinins
	Pneumococcal polysaccharide 0.16 mg. Types I and II antigen	no titer—no ppt. 0 mg. antibody N.	no titer—no ppt. 0 mg. antibody N.
W.A. 7-year-old male	Diphtheria—7 injections 0.5 cc. DPT antigen over 2-month period	Schick positive	Schick positive
	2,000 million typhoid org., 1,000 million paratyphoid org. i.d., subcut., and i.v. over 4-week period	no titer H, O, or B agglutinins	no titer H, O, or B agglutinins
T.A. 5-month-old male	1,500 million typhoid organisms, 750 million paratyphoid org. i.d., subcut. over a 5-week period	no titer H, O, or B agglutinins	no titer H, O, or B agglutinins

lation, blood samples were drawn and appropriate tests for antibody formation carried out. Whereas control subjects responded regularly and vigorously to these antigenic stimuli, none of the 5 patients with agammaglobulinemia tested exhibited an antibody response. Subsequent attempts to induce antibody formation by secondary antigenic stimulation, anamnestic response, likewise failed. Electrophoretic and turbidimetric analysis of blood samples taken serially throughout the period of antigenic stimulation and for several weeks thereafter revealed no evidence of gamma globulin accumulation as a consequence of these stimuli.

Table 7 summarizes results of a study of the titers of isoagglutinins against heterologous blood cells in agammaglobulinemic and normal persons. Of our patients, 4 were of blood group O. Behaving normally, each would be expected to possess antibodies against both A and B cells. Instead, none of the 4 possessed antibodies against either antigen. The other 3 patients, 1 adult and 2 infant siblings, were of blood group A, and, if normal, would be expected to have a high titer of antibody versus B cells and no titer versus A cells. In each of these patients, a very low but definite concentration of isoagglutinin against B cells was observed. In no instance, however, did the concentration of isoagglutinin overlap the lowest normal readings obtained in our laboratory. Included for comparison are the geometric mean titers obtained on groups of patients representing O, A, and B blood groups.

TABLE 7
BLOOD GROUP AND REACTION TO HETEROLOGOUS BLOOD GROUP CELLS IN PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Blood group*	*Isoagglutinin titer*	
		Anti A	*Anti B*
E.S.	O	no titer	no titer
L.L.	O	"	"
W.A.	O	"	"
T.A.	O	"	"
F.H.	A	–	+ in 1-2 dilution
F.T.	A	–	+ in 1-5 dilution
T.T.	A	–	+ in 1-5 dilution
Normal Group O 20 cases	O	1:343.0*	–
Normal Group A 18 cases	A	–	1:179.6*
Normal Group B 5 cases	B	1:139.3*	–

*Geometric mean titer.

TABLE 8
ISOAGGLUTININ TITERS IN NORMAL CHILDREN

Patient	*Age*	*Sex*	*Blood type*	*Isoagglutinin titers*	
				Anti A	*Anti B*
R, C.A.	12	F	O	1-1,280	
H, R.	14	M	O	1- 320	
G, W.	15	M	O	1- 640	
M, D.	7	M	O	1- 320	
Z, D.	7	F	O	1- 640	
M, B.	6	F	O	1- 320	
J, L.	13	M	O	1- 640	
B, J.	24	F	O	1- 160	
H, F.	3	F	O	1-1,280	
E, J.	2½	M	O	1- 160	
W, D.	8½	M	O	1- 320	
B, D.	8	M	O	1- 160	
M, K.	20 mo.	F	O	1-1,280	
B, J.	11	F	O	1- 40	
P, H.	30	M	O	1- 640	
K, W.	2	M	O	1- 160	
Y, C.	3	M	O	1- 640	
W, R.	3	M	O	1- 640	
H, V.	14 mo.	F	O	1- 40	
H, V.	2	M	O	1- 320	
A, J.	12	F	A		1- 160
K, P.	11	F	A		1- 640
S, D.	12	M	A		1- 320
S, D.	10	M	A		1- 40
M, R.	7	M	A		1- 160
V	9		A		1-1,280
M, T.	6	M	A		1-1,280
P, A.	24	M	A		1- 640
G, R.	31	M	A		1- 20
C, D.	28	M	A		1- 40
D, R.	12	M	A		1- 640
R, E.	8	F	A		1- 640
P, M.	11	F	A		1- 40
B, R.	9	M	A		1- 320
B, B.	4	M	A		1- 640
H, L.	2	M	A		1- 20
C, R.	15 mo.	M	A		1- 640
E, M.	3	M	A		1- 5
S, K.	10	F	B	1- 320	
W, J.	11	F	B	1- 320	
N, R.	5	M	B	1- 20	
W, J.	15	M	B	1- 40	
M, L.	3	F	B	1- 640	

For further comparison, data on the actual isoagglutinin titers of a group of other hospitalized patients and normal persons is recorded in table 8.

To further test the immunologic handicap in agammaglobulinemic patients, an attempt was made to immunize 5 of them to heterologous blood group cells by the parenteral injection of washed heterologous cell concentrates. Mismatched cells were injected subcutaneously, intramuscularly, and intravenously in varying amounts. The experimental details and results obtained are summarized in table 9. In no instance was any systemic reaction produced by the injection of these cells and in no instance was clear evidence of antibody production in response to this antigenic challenge observed. In the adult male of group A who showed a low but consistent microscopic agglutination of group B cells on microscopic examination of the 1 to 2 serum dilution preparation, a questionable rise of one tube to 1 to 4 concentration was recorded ten days after injection of "mismatched" cells. This finding supports the conclusion drawn from preceding data that the "immunologic paralysis" in this individual was incomplete. It is our contention then that this patient has been set aside from the others studied. Although he too has a profound immunologic handicap, the

TABLE 9

ANTIBODY RESPONSE TO INJECTION OF CELLS OF HETEROLOGOUS BLOOD GROUP IN PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Blood group*	*Cells injected*	*Initial titer*	*Days after antigen injection* 5	10	15	20
E.S. First stimulation	O	5 cc. group A i.m. 5 cc. group A i.v. 2 cc. group A sc. packed cells	no titer	no titer	no titer	no titer	no titer
E.S. Second stimulation	O	*15 cc. packed group A cells i.v.	"	"	"	"	"
L.L. First stimulation	O	10 cc. group AB cells i.v.	"	"	"	"	"
L.L. Second stimulation	O	15 cc. group A cells i.v.	"	"	"	"	"
W.A.	A	3 cc. group A cells sc. and i.m.	"	"	"	"	"
		3 cc. group A cells i.v.	"	"	"	"	"
T.A.	O	3 cc. group A cells	"	"	"	"	"
		2 cc. group B cells i.v.					
F.H.	A	$\frac{1}{2}$ cc. group B cells i.v.	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$

deficiency is less severe than that of the other patients and might be descriptively referred to as an "immunologic paresis" rather than "immunologic paralysis."

It has been observed repeatedly that the sequence of clinical diseases which threaten the life of patients with agammaglobulinemia has its basis in bacterial infection. Repeated attacks of pneumococcal pneumonia, bacterial meningitis, bacterial infections of the middle ear, bacterial disease of the paranasal sinuses and of the urinary and gastrointestinal tract were observed regularly. Strangely enough, virus infections appear to be handled efficiently and normally by these patients. Study of our cases supports the observation[17] that in spite of the immunologic handicap, virus infections do not occur repeatedly and are not unusually severe in patients with congenital agammaglobulinemia. Our observations support the conclusion that adults with acquired agammaglobulinemia likewise handle certain virus infections satisfactorily and have clinical illness based almost entirely on the recurrence of severe life threatening bacterial infections. (Since this manuscript was prepared for publication, the 58-year-old man died with acute yellow atrophy of the liver presumed to be due to either infectious hepatitis or homologous serum hepatitis. This observation taken together with the finding of Keiden and associates[38] suggests that with certain virus infections the immunologic abnormality represents a clinically significant handicap.) Just as in the children, it is recurrent bouts of pneumococcal pneumonia, recurrent attacks of pneumococcal meningitis, recurrent episodes of middle ear and paranasal sinus disease, as well as recurrent instances of bacterial septicemia that result in the clinical syndrome characteristic of adult patients with agammaglobulinemia. Chickenpox, poliomyclitis, mumps, and measles all have been observed in our cases. In each instance the disease has run an essentially normal course and recovery has occurred in the usual fashion. There is no evidence that any of these patients have inordinately frequent attacks of the common cold, acute respiratory disease, atypical pneumonia, influenza, or other diseases representing the common virus infections. One of our patients, a 7-year-old boy, E. S., who had been shown to have no circulating antibodies and no antibody response, was intimately exposed to rubeola on 3 different occasions during a nine-month period of hospitalization. He did not develop measles. This observation can only be interpreted as evidence of substantial resistance to this highly contagious virus disease in the complete absence of gamma globulin or capacity to form antibody.

The severe necrotizing reactions after injection of vaccinia virus in patients who have an immunologic handicap[38, 39] have served to dissuade us from vaccinating our agammaglobulinemic patients. However, others have vaccinated children with agammaglobulinemia. Janeway reported apparently successful uncomplicated vaccination of 6 cases of agammaglobulinemia and 2 of our children have been vaccinated by other physicians without untoward event. In 1 of our patients, a 7-year-old boy, 3 attempts at vaccination resulted in no response whatever. Whether this result expresses inadequacy of the vaccine administered or lack of reactive capacity of the host has not been determined and requires further study. In another case, W. A., mild, generalized vaccinia was followed in a few days by spontaneous recovery and was recorded as a result of vaccination.

In an attempt to make sense of the paradoxic behavior of agammaglobulinemic patients toward antigenic stimulation on the one hand and virus infections on the other and to determine whether the immunologic handicap of the patients with agammaglobulinemia includes failure to respond to virus and rickettsial antigens, intensive stimulation was provided with influenza, poliomyelitis, mumps, spotted fever, Q fever, typhus, W.E.E., and poliomyelitis antigens. As indicated in table 10, no significant response occurred to any of these antigenic agents. If we explain the initial presence of low concentration of hemagglutina-

TABLE 10
RESPONSE OF PATIENTS WITH AGAMMAGLOBULINEMIA TO STIMULATION WITH VIRUS AND RICKETTSIAL ANTIGENS

Antigen used	*E.S.*	*Patient W.A.*	*F.H.*
Influenza	no response	insig. response	no response
Mumps virus	"	no response	"
Spotted fever group antigens	"	"	"
Q fever	"	"	"
Typhus fever	"	"	"
W.E.E.	"	"	"
Polio virus	"	"	minimum but definite response

tion inhibitor against influenza virus as a reflection of the natural nonspeeific hemagglutination inhibitors of Ginsburg,[40] no antibodies were present and no antibody response occurred after injeetion of any of the virus antigens. In 2 of the ehildren, neither primary nor seeondary stimulation with polio or mumps virus resulted in speeifie antibody produetion. The 58-year-old man, who had no antibodies against the polio viruses initially, developed minimum evidenee of neutralizing antibodies against type I virus after 3 injeetions of Salk antigen. These data are interpreted as further evidenee of the immunologie handieap eharaeteristie of these patients. Coupled with elinieal observations they must also be interpreted as evidenee that anaphylactic type antibody is not essential for the symptomatology eharaeteristic of eertain virus diseases and that reeovery from some virus infeetions may be aeeomplished without the aid of antibodies. Clinieal evidence taken together with these observations also suggests that reinfection with virus agents may indeed be inhibited by means other than eirculating antibodies. On the other hand, it is possible that these findings indicate that patients with agammaglobulinemia, although lacking in circulating antibodies, do indeed possess antibodies bound to the cells or otherwise retained in the tissues which provide them a measure of proteetion against the obligate cellular parasitism represented by virus infeetion. Studies to clarify this relationship are in progress. A final possible explanation is that all patients so far diseovered have in reality extreme hypogammaglobulinemia of varying severity, some gamma globulin in however small amounts being present in all of them. If this is the case, possibly defense against virus infeetion requires only minute amounts of gamma globulin, whereas bacterial infection requires much more.

Table 11 summarizes data obtained in an attempt to determine whether patients with agammaglobulinemia develop bacterial-type hypersensitivity in response to baeterial products. The evidenee presented unfortunately does not provide an unequivoeal answer. One of the ehildren, W. A., developed erythema without induration which lasted several days after the intradermal injection of tubereulin. This same reaetion was, moreover, observed several times with 3 different eoneentrations of old tubereulin. Beause of the duration of the erythema, it has been tempting to reeord this as a positive Mantoux reaetion and as conclusive evidenee that in this patient we have observed a elear dissoeiation of baeterial-type hypersensitivity and elassical immune body formation. Induration, however, is an essential part of a truly positive tubereulin reaction. The eomplete absenee of induration in

TABLE 11
DELAYED (BACTERIAL-TYPE) HYPERSENSITIVITY TO BACTERIAL PRODUCTS IN PATIENTS WITH AGAMMAGLOBULINEMIA

Test performed	*F.H., 58-year-old male*	*E.S., 7-year-old male*	*Patient T.A.*	*L.L.*	*W.A.*	*F.T.*	*T.T.*
Tubereulin							
1-10,000	neg	neg	neg	neg	?+	neg	neg
1-1,000	neg	neg	neg	neg	?+*	neg	neg
1-100	neg	neg	neg	neg	?+	neg	
1-10	neg	neg	neg	neg	neg		
P.P.D.							
1st strength	neg	neg	neg	neg	neg	—	—
2nd strength	neg	neg	neg	neg	?+		
SK-SD							
10 units SK	neg	neg	neg	neg	neg		
100 units SK	neg	neg	neg	neg	neg	—	—
1000 units SK	±	neg	neg	—	neg		
Whole Group A strep vaccine	neg	neg	—	neg	neg	—	—
Whole pneumococcus vaccine	neg	neg	—	neg	neg	—	—

*No induration—slight erythema lasting 48 to 72 hours.

this instance prohibits our classifying this reaction as a clear example of bacterial-type hypersensitivity. Another observation was provocative. Minimum erythema and induration occurred after intradermal injection of 1,000 units streptokinase and 250 units streptodornase intradermally in F. H., the 58-year-old man. The fact, however, that this reaction occurred only with a very concentrated preparation of SK-SD and not at all with the lower dilutions, as well as the fact that it developed only in the patient in whom we had already demonstrated the existence of minimum immunologic responsiveness detracts from its significance and makes the observation difficult to interpret. Zinneman[41] has observed an adult male with agammaglobulinemia to have a truly positive Mantoux. This observation like the latter is of questionable significance, since most adults with agammaglobulinemia suffer from immunologic paresis rather than paralysis and no current immunologic theory necessitates the production of large amounts of antibody to explain bacterial-type hypersensitivity.

Contrariwise, as a group, the patients with agammaglobulinemia differ strikingly from the normal population in their reactivity to streptococcal antigens. Of normal children, 75 to 100 per cent of those 7 years of age or older show delayed bacterial-type hypersensitivity against streptococcal products. In contrast, none of the patients with agammaglobulinemia gave clear evidence of hypersensitivity to the streptococcal antigens used. The results of this study are summarized in table 12. It must be concluded from these observations that patients with agammaglobulinemia have difficulty developing bacterial-type hypersensitivity. This deficiency is probably based on the same mechanism as that responsible for their handicap in producing circulating antibodies.

Finally, in order for the data on immune reactions to be interpretable without reservation, it was deemed necessary that the concentration of complement in the serums of these patients be recorded. Consequently, complement concentrations were determined according to the method of Wedgewood and Janeway in 5 of the patients. In table 13 these data are summarized. For these estimates, blood samples were drawn into sterile tubes, placed in the refrigerator to clot, separated in a refrigerated centrifuge at 4°C. and stored at −70°C. in sealed containers until used. As the table shows, concentration of complement measured this way is normal for each patient studied.

TABLE 12
DELAYED (BACTERIAL-TYPE) HYPERSENSITIVITY VERSUS STREPTOCOCCAL PRODUCTS IN CHILDREN

Vaccine injected I.D.	*Group*	*Number*	*Number positive*	*Number negative*	*%+*
Streptokinase 10 u. Streptodornase 2.5 u. in 0.1 cc. saline	Agammaglobulinemia	5	0	5	0%
"	Hospitalized children 7 to 16 yrs. of age	24	23	1	97%
"	Hospitalized children 2 to 7 years of age	15	8	7	53%
"	Normal adults	16	14	2	88%

TABLE 13
SERUM COMPLEMENT CONCENTRATIONS IN PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Complement concentration units per cc.*	*Classification of syndrome*
E.S. 7-year-old male	62.0	"immunologic paralysis" complete, congenital
F.H. 58-year-old male	80.0	"immunologic paresis" acquired
W.A. 7-year-old male	96.0	"immunologic paralysis" complete, congenital, familial
T.A. 6-month-old male	80.0	"
Normal value	60-75 units	normal
Wedgewood & Janeway	mean 47.7 units	"

We must conclude from these observations that all of the patients with agammaglobulinemia whom we have investigated show a profound immunologic handicap. In 4 of them, 3 children and 1 adult, no evidence of capacity to form antibodies of any kind has been obtained. We conclude that these 4 patients have a true immunologic paralysis. Of the remaining 3 patients, 2 young male siblings with congenital disease have not been thoroughly studied, but appear to be able to form small amounts of antibodies against heterologous blood group antigen. A third patient, who has been thoroughly studied, appears to suffer only from severe "immunological paresis." He possessed low-titer antibodies against heterologous blood group cells, formed small amounts of antibody against heterologous blood cells and polio virus, and had low degree of skin reactivity against streptococcal antigens.

HEMATOLOGIC OBSERVATIONS IN PATIENTS WITH AGAMMAGLOBULINEMIA

Although Young and Wolfson,[21, 22] Keidan and associates,[38] and Rohn and associates[24] have suggested that agammaglobulinemia may be a

disturbance of protein synthesis associated with a failure of lymphocyte production, no thorough hematologic study has been conducted in patients with this disease. The latter authors reported reduced numbers of lymphocytes as a characteristic feature of the circulating blood in their patients with agammaglobulinemia. In contradistinction to this observation, none of the 7 patients studied in our laboratory had lymphopenia. Instead, as is shown in table 14, morphologically normal lymphocytes were present in at least normal numbers in both blood and bone marrow of these patients. Several hematologic abnormalities were observed, however, which pressed us to investigate thoroughly the hematopoietic tissues in patients with agammaglobulinemia. Further, our longstanding interest in the cellular basis of gamma globulin and antibody production[42-48] led us to study the response of the hematopoietic tissues of these patients to antigenic stimulation. Comparison of bone marrow and lymph node changes of normal and agammaglobulinemic subjects after both primary and secondary antigenic stimulation was made. The data obtained from the extensive hematologic analysis permit the conclusion that patients having agammaglobulinemia regularly show evidence of profound disturbance of the hematopoietic reticulum. We have found, for example, that these patients:

1. Regularly exhibit a deficiency of plasma cells in their hematopoietic centers and in their inflammatory exudates. This deficiency amounts to virtual absence of plasma cells in those having immunologic paralysis.
2. Regularly fail to respond to even the most intensive antigenic stimulation with either antibody production or plasma cell formation.
3. May respond to bacterial infection with extreme leukocytosis.
4. May develop without apparent cause episodes of transient neutropenia, persistent neutropenia, or even apparent cyclic neutropenia.

TABLE 14
NUMBERS OF LYMPHOCYTES IN PERIPHERAL BLOOD IN PATIENTS WITH AGAMMAGLOBULINEMIA*

Patient	*Total lymphocytes per mm³X*	*% Lymphocytes in bone marrow†*
E.S.	4575	19.6
W.A.	4322	25.8
T.A.	6055	15.0
F.T.	2993	17.8
T.T.	7961	10.0
L.L.	4654	29.4
F.H.	2729	43.4

*Calculated from total leukocyte count and percentage distribution of cells.
†Based on 500 cell differential count of the direct aspirate of the bone marrow.

These latter hematologic disturbances cannot, in some instances, be related to either bacterial or virus infections.

In addition to these observations, several other hematologic disturbances have been found to exist in our patients. In F. H., the adult male having "acquired agammaglobulinemia," the disease developed in apparent association with the occurrence of a large thymoma. The latter tumor was morphologically representative of a benign but intensive local proliferation of thymocytes and reticulum cells. In this same patient, study of the bone marrow and peripheral blood revealed virtual absence of eosinophils and their recognizable precursors.

The adult female who also has acquired agammaglobulinemia developed, after the apparent onset of her illness, a profound morphologic disturbance of the reticular tissues featured by extensive proliferation of the fixed and free reticulum cells in the spleen, lymph nodes, and bone marrow. This reaction was reflected clinically in splenomegaly and lymphadenopathy due primarily to the reticular proliferation. In addition to extensive reticular hyperplasia, however, granulomata (without plasma cells) not further defined by the pathologist, were observed in the spleen and lymph nodes of the latter patient. In

TABLE 15
WHITE BLOOD COUNTS ON PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Sex*	*Age*	*Hemoglobin gm.%*	*Total leukocytes*	*Neutrophils no./cu. mm.*	*Lymphocytes no./cu. mm.*	*Monocytes no./cu. mm.*	*Eosinophils no./cu. mm.*	*Basophils no./cu. mm.*
E.S.	M	7 yr.	12.4	9,150	3,250	4,575	91	91	91
W.A.	M	7 yr.	13.1	24,900	19,414	4,233	249	0	0
T.A.	M	5 mo.	10.5	10,400	2,912	6,055	175	58	0
L.L.	F	26 yr.	12.4	8,950	3,128	4,654	259	179	0
F.H.	M	58 yr.	16.0	12,300	8,856	2,729	492	0	123
F.T.	M	20 mo.	9.9	4,100	205	2,993	820	411	0
T.T.	M	15 mo.	11.3	9,150	549	7,961	640	0	0
J.S.	M	7 mo.	12.1	14,500	2,175	11,745	435	145	0

TABLE 16
BLOOD COUNTS ON AGAMMAGLOBULINEMIA DURING ACUTE DISEASE

Patient	*Infection*	*Total leukocytes*	*Neutrophils*	*Lymphocytes*	*Monocytes*	*Eosinophils*	*Basophils*
E.S.	pneumococcal meningitis	77,100	74,787	2,313	0	0	0
F.H.	staphylococcus septicemia	15,600	11,104	1,872	312	0	156
L.L.	pneumococcal pneumonia	68,487	59,584	7,534	1,369	0	0
W.A.	pneumonia (bacterial?)	24,500	18,865	4,410	980	0	245
T.A.	none	6,600	132	6,204	264	0	0
T.T.	pneumonia	12,900	645	10,707	387	1,161	0
F.T.	pneumonia	4,775	183	3,065	778	458	92

this instance the peripheral blood, except for vigorous neutrophilic response during infection, always either was normal or showed slight lymphocytosis.

Table 15 summarizes white blood counts on all 8 of the patients with agammaglobulinemia. The wide variations in the peripheral count in these patients is reflected in these data. Increased normal or near normal numbers of lymphocytes were present in every instance. In none of these patients was lymphopenia observed. Observations of the leukocytes in the peripheral blood of these patients during acute infections were even more provocative, table 16. Four of the patients responded to infection with leukocytosis, sometimes extreme, while in the other 3, pronounced neutropenia was present at the time infection occurred.

In figure 2, curves reflecting changes in neutrophil counts in 1 of the patients who suffered from agammaglobulinemia, apparent immunologic paresis, and apparent cyclic neutropenia are recorded. During the episodes of neutropenia, the bone marrow of this patient showed a substantial shift to the left and failure of maturation of the cells of the neutrophilic series.

In figure 3, similar curves for the sibling of the patient are plotted. This patient's hematologic disturbance was featured by persistent rather than cyclic neutropenia. Splenectomy had no influence on either the course of the disease or the degree of neutropenia. This child, as well as his brother, showed evidence of failure of neutrophilic maturation in the bone marrow at the time the neutrophilia was most pronounced.

Figure 4 illustrates the development of profound neutropenia in another of the agammaglobulinemic children. This patient had agammaglobulinemia with "immunologic paralysis." The neutropenia, dismissed when it occurred in several of the other agammaglobulinemic children as a possible reflection of bacterial or viral trauma

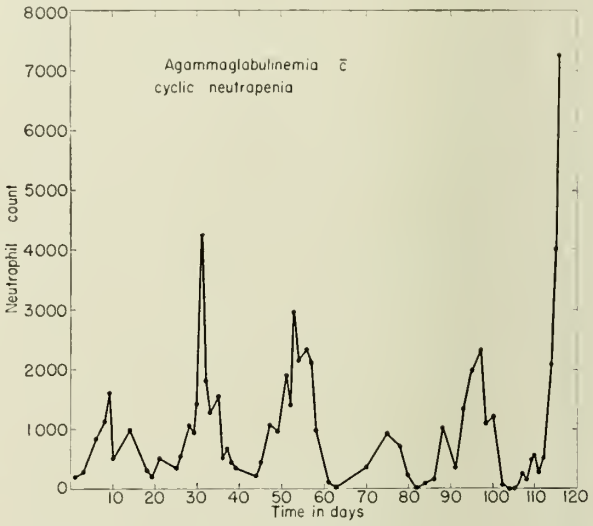

Fig. 2. Curves reflecting changes in neutrophil counts in a patient with agammaglobulinemia, apparent immunologic paresis, and apparent cyclic neutropenia.

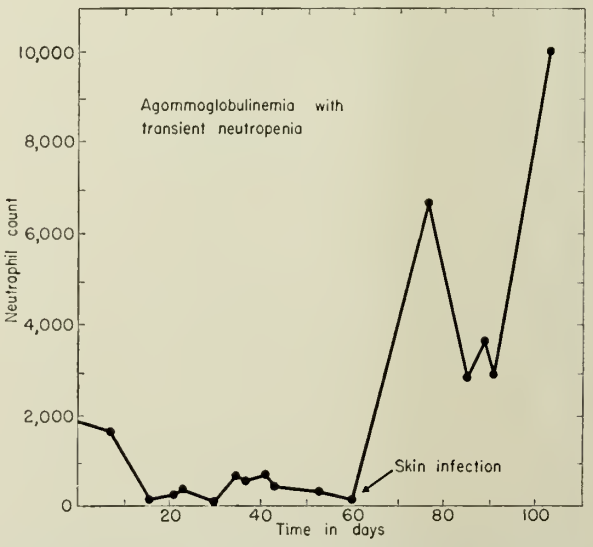

Fig. 3. Curves reflecting changes in neutrophil count of sibling of patient depicted in figure 2. Note persistent neutropenia.

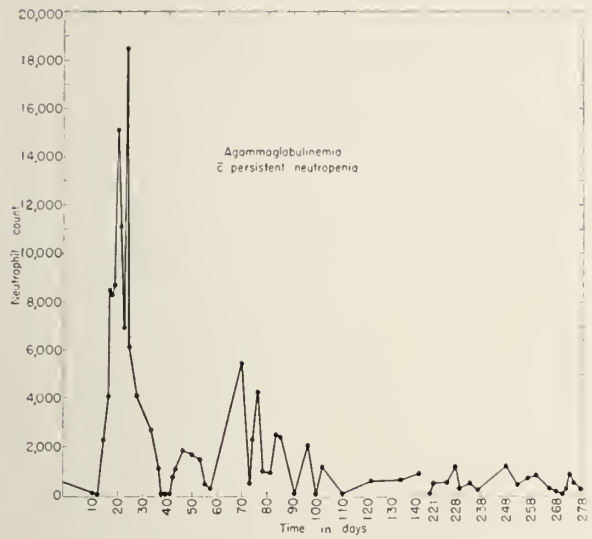

Fig. 4. Development of profound neutropenia in an agammaglobulinemic child. Note prolonged period of neutropenia.

to the hematopoietic tissues, developed in this instance in the apparent absence of infection. At the present writing, this child, after having had a persistent neutropenia for approximately two months, has normal numbers of circulating neutrophils. It is impossible at the moment to ascertain whether his hematologic disturbance will be transient as was the case on several occasions with his older sibling, and another child, E. S., will be cyclic as in F. T., or will be persistent as in T. T. Thus, at one time or another, 5 of the agammaglobulinemic children have suffered from profound neutropenia, cyclic in 1 instance, apparently persistent in 2, and transient in 2 others.

As previously mentioned, F. H., a 58-year-old male with acquired agammaglobulinemia, possessed almost no eosinophils in either the peripheral blood or bone marrow. This observation prompted a thorough evaluation of the eosinophil content of the blood and bone marrow in the other patients with agammaglobulinemia. In each patient 500-cell differential counts of the peripheral blood smears were made, and total number of eosinophils was calculated from the total white blood count and the percentage of eosinophils. Similarly for the eosinophils in the bone marrow, the percentage figure is based on the routine 500-cell count. The results are summarized in table 17.

The results of this study indicate that eosinophils are developing normally in most of the patients with agammaglobulinemia and show further that eosinophilia may occur in the absence of circulating antibody or gamma globulin if appropriate stimulation is available (F. T.). (Since this manuscript was prepared, another of the agammaglobulinemic patients, W. A., has developed pronounced eosinophilia associated in this instance with staphylococcal infection and bronchiectasis. Wheezing and bronchospasm were among the clinical manifestations of this episode. However, asthmatic manifestations did not respond to treatment with epinephrine, ephedrine or aminophyllin, and both the respiratory symptoms and eosinophilia subsided on treatment with Chloromycetin.)

The observation of extreme eosinopenia on hematologic analysis of the blood and bone marrow of one of our patients with agammaglobulinemia and of lymphopenia in several other instances coupled with the knowledge that cortisone and 17-hydroxycorticosterone enhance infection,[49] inhibit antibody production,[50] and decrease gamma globulin concentration under certain circumstances,[51] prompted investigation of pituitary adrenal function in these patients. Total absolute eosinophil counts performed after the method of Randolf[52] and 17-hydroxycorticosteroid concentration measured by the method of Nelson and Samuels[53] formed the core of this study. The eosinophil and 17-hydroxycorticosteroid concentrations were determined initially and again two and four hours after stimulation with 25 mg. of ACTH in each of 4 patients with agammaglobulinemia. The results are recorded in table 18. Here again may be seen that with absolute eosinophil counts, normal numbers of eosinophils are present in all except one of the patients studied prior to administration of ACTH. All 4 patients had normal concentrations of 17-hydroxycorticosteroids in the initial blood sample. Stimulation with ACTH produced a sharp fall in eosinophils and a significant rise in 17-hydroxycorticosteroids in every instance. These data are interpreted as indicating that the pituitary adrenal axis is functioning normally in

TABLE 17
EOSINOPHILS IN BLOOD OF PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Peripheral blood* *No. eosinophils per cu. mm**	*Bone marrow* *Mature eosinophils %†*	*Bone marrow* *Eosinophilic precursors %†*
F.H.	0	0	0
E.S.	247.0	1.8	3.0
W.A.	170	4.6	4.2
T.A.	256.6	2.0	2.0
L.L.	179.0	1.4	1.4
F.T.	1283.0	3.0	9.2
T.T.	127.0	1.2	1.4

*Based on 500-cell differential counts of blood cells and the total white count.
†% of nucleated bone marrow cells.

TABLE 18

RESPONSE OF EOSINOPHILS AND 17 HYDROXYCORTICOSTEROIDS IN PATIENTS WITH AGAMMAGLOBULINEMIA*

Patient	Eosinophil count† Before ACTH	Eosinophil count† 2 hours after ACTH	Eosinophil count† 4 hours after ACTH	17 Hydroxycorticosteroids‡ Before ACTH	17 Hydroxycorticosteroids‡ 2 hours after ACTH
F.H., 58-year-old man	0	0	0	15.8	38.6*
E.S., 7-year-old boy	162	119	28	6.5	33.7
W.A., 7-year-old boy	328	147	75	18.5	46.1
T.A., 6-mo.-old boy	303	197	58	8.5	38.7
Normal child	249	104	24	10.2	32.0

*This study was performed with the assistance of Dr. V. C. Kelley, department of pediatrics, University of Utah, Salt Lake City.
†Determined by direct chamber counting technic of Randolf.
‡Determined according to the method of Nelson and Samuels.

patients with agammaglobulinemia. They would also seem adequate to eliminate adrenal malfunction as a possible explanation for the syndrome under investigation.

RESPONSE OF BONE MARROW OF NORMAL CHILDREN AND AGAMMAGLOBULINEMIC PATIENTS TO ANTIGENIC STIMULATION

Table 19 records results of bone marrow analysis of each of 7 agammaglobulinemic patients. The percentages of various cellular elements recorded in the table represent values obtained from 500 cell counts on direct smears of the marrow. Data obtained from analysis of the bone marrows of 12 normal children and Wintrobe's normal values for adults are included for comparison. Abnormalities in the cellular distribution within the bone marrow were observed in each patient. For example, none of these patients showed plasma cells on the routine 500-cell count. In addition, a tendency toward increased numbers of reticulum cells was observed in several instances. Further, the forementioned deficiency in development along eosinophil lines was present in 1 case, F. H., and an arrest in the development of neutrophils in 2 of the patients, F. T. and T. T., was noted. The plasmacytic deficiency was, however, the only consistent abnormality detected on study of the bone marrow. As for the lymphocytes, their concentration in the marrow in our patients was not decreased in any instance. To the contrary, normal numbers or increased percentages of these elements featured the marrow analysis in all patients with agammaglobulinemia.

To gain more incisive evidence on the nature of the hematologic anomaly in patients with agammaglobulinemia, comparison of morphologic changes induced in the bone marrow by antigenic stimulation of normal children and agam-

TABLE 19

RELATIVE NUMBERS OF BONE MARROW CELLS IN 7 PATIENTS WITH AGAMMAGLOBULINEMIA*

Patient	Myeloblast	Promyelocyte	Neutrophilic myelocyte	Neutrophilic metamyelocyte	Mature neutrophil	Eosinophilic myelocyte	Eosinophilic metamyelocyte	Mature eosinophil	Basophilic myelocyte	Basophilic metamyelocyte	Mature basophil	Lymphocyte	Megakaryocyte	Reticulum cells	Plasma cells	Pronormoblast	Normoblast
E.S. 7-year-old male	0.4	5.2	10.2	21.4	18.0	1.4	0.6	1.0	0.0	0.0	0.2	19.6	0.4	8.0	0.0	2.0	13.4
L.L. 26-year-old female	1.0	5.2	8.8	18.4	19.6	2.4	2.0	2.4	0.0	0.0	0.0	25.8	0.4	4.8	0.0	1.6	7.8
F.H. 58-year-old male	1.4	8.6	13.0	22.8	21.0	0.0	0.0	0.2	0.4	0.0	0.4	15.0	0.4	2.4	0.0	2.0	12.4
W.A. 7-year-old male	0.8	6.4	10.2	23.6	9.8	1.6	1.8	1.6	0.0	0.2	0.2	17.8	0.2	2.8	0.0	2.8	20.2
T.A. 5-month-old male	1.2	6.6	13.6	24.8	19.6	0.8	1.2	2.0	0.2	0.0	0.2	10.0	0.2	4.2	0.0	4.0	11.4
F.T. 20-month-old male	2.0	8.2	4.2	9.4	0.4	3.0	3.2	4.0	0.4	0.4	0.6	29.4	1.0	9.8	0.2	2.6	21.2
T.T. 15-month-old male	2.6	5.8	3.2	6.4	4.0	1.4	1.4	2.2	0.0	0.2	0.2	43.4	0.0	13.6	0.0	1.4	14.2
13 normal children (Mean)	1.25	4.50	16.33	30.10	10.20	2.02	1.51	1.15	0.48	0.32	0.28	10.08	0.43	1.66	0.41	1.96	17.27
(Range)	0.7-2.2	3.0-6.0	8.4-23.4	21.8-35.8	3.7-14.6	0.8-3.6	0.6-2.6	0.4-2.2	0.0-1.4	0.0-1.0	0.0-0.6	4.4-17.0	0.2-1.0	0.4-3.0	0.0-1.0	0.6-3.0	11.0-4.0
(Mean)	2.0	5.0	12.0	22.0	20.0	1.5	—	2.0	0.3	—	0.2	10.0	0.4	2.2	0.4	4.0	18.0
Normal Adults (Range) Wintrobe	0.3-5.0	1.0-8.0	5.0-19.0	13.0-32.0	7.0-30.0	0.5-3.0	—	0.5-4.0	0.0-0.5	—	0.0-0.7	3.0-17.0	0.3-3.0	0.7-7.0	0.0-2.0	1.0-8.0	7.0-32.0

*Each figure represents the percentage of the particular cellular element in direct smears made of the marrow aspirate as determined by counts of 500 nucleated cells.

TABLE 20

RESPONSE OF BONE MARROW OF NORMAL AND AGAMMAGLOBULINEMIC PATIENTS TO INTENSIVE ANTIGENIC STIMULATION

	Patient	Myeloblast	Promyelocyte	Neutrophilic myelocyte	Neutrophilic metamyelocyte	Mature neutrophil	Eosinophilic myelocyte	Eosinophilic metamyelocyte	Mature eosinophil	Basophilic myelocyte	Basophilic metamyelocyte	Mature basophil	Lymphocyte	Megakaryocyte	Reticulum cells	Plasma cells	Pronormoblast	Normoblast
Normal children	R.L. 10-year-old male before antigen	1.0	5.0	17.0	22.2	23.4	1.8	1.0	1.6	0.4	0.2	0.0	9.6	0.2	1.8	0.4	2.0	12.4
	after antigen	0.4	6.6	8.0	26.6	15.8	4.0	1.8	3.4	0.4	0.4	0.2	12.0	0.4	1.8	2.4	1.4	15.4
	R.A. 7-year-old female before antigen	0.6	2.4	6.0	23.6	16.4	1.4	1.4	1.0	0.2	0.2	0.2	23.2	0.0	2.4	0.4	1.2	19.4
	after antigen	1.6	4.6	10.6	23.6	13.4	1.0	1.4	1.6	0.4	0.2	0.4	15.2	0.2	2.4	1.4	2.2	20.0
	W.O. 7-year-old male before antigen	1.6	3.2	8.0	18.2	16.8	3.4	2.0	3.4	0.2	0.2	0.6	15.4	0.6	4.0	0.4	0.4	18.4
	after antigen	0.8	4.6	6.8	19.6	8.6	2.8	2.4	3.4	0.4	0.2	0.0	11.6	0.8	3.2	2.6	3.4	28.8
	K.O. 8-year-old female before antigen	0.6	3.4	8.0	18.8	17.4	1.4	1.4	1.6	0.2	0.4	0.4	11.4	0.2	1.4	0.4	1.8	24.4
	after antigen	1.0	4.8	9.8	14.8	19.4	3.8	3.0	1.8	0.8	0.2	0.2	15.8	0.2	4.4	3.4	2.0	14.2
Agammaglobulinemic patients	F.H. 58-year-old male before antigen	1.4	8.6	13.0	22.8	21.0	0.0	0.0	0.0	0.4	0.0	0.4	15.0	0.4	2.4	0.0	2.0	12.4
	after antigen	0.8	4.4	13.0	20.6	12.0	0.0	0.0	0.2	0.8	0.0	0.2	18.4	0.4	1.4	0.0	4.8	22.6
	E.S. 7-year-old male before antigen	0.4	5.2	10.2	21.4	18.0	1.4	0.6	1.0	0.0	0.0	0.2	19.6	0.4	8.0	0.0	2.0	13.4
	after antigen	0.6	4.6	11.8	27.6	22.0	1.4	1.2	1.8	0.4	0.2	0.4	13.0	0.2	2.6	0.0	1.4	10.8
	L.L. 26-year-old female before antigen	1.0	5.2	8.8	18.4	19.6	2.4	2.0	2.4	0.0	0.0	0.2	25.8	0.4	4.8	0.0	1.6	7.8
	after antigen	1.0	5.4	9.4	19.0	20.8	1.4	0.8	2.4	0.0	0.0	0.4	21.6	0.4	5.8	0.0	2.2	9.4
	W.A. 7-year-old male before antigen	0.8	6.4	10.2	23.6	9.8	1.6	1.8	1.6	0.0	0.2	0.2	17.8	0.2	2.8	0.0	2.8	20.2
	after antigen	1.2	5.8	7.4	18.8	12.6	1.6	3.0	4.6	0.0	0.0	0.4	18.0	0.6	4.2	0.0	0.0	19.2

maglobulinemic patients was carried out. Recorded in table 20 are results of a study of bone marrow obtained immediately prior to antigenic administration and after three weeks intensive stimulation with typhoid-paratyphoid vaccine in normal children and patients with agammaglobulinemia. Whereas each of 4 normal children developed significant marrow plasmacytosis in response to this stimulation, the 4 patients with agammaglobulinemia did not. No other consistent changes occurred in the marrow as a consequence of the repeated injections of antigen in either group. The failure of the plasmacytic response in patients with agammaglobulinemia is even more striking when large enough numbers of marrow cells are counted so that stable figures for plasma cell percentages are obtained. In table 21, the numbers of plasma cells in the bone marrow of normal children and agammaglobulinemic patients based on repeated 5,000-cell counts are recorded. It may be seen that in each of the agammaglobulinemic patients studied, a gross deficiency of this cellular element exists. In table 22, the plasma cell and antibody responses of 4 normal children and 4 agammaglobulinemic patients are compared. A sharp rise in the plasma cell content of the bone marrow occurred in each instance along with the development of high antibody titer against the antigen injected. Not so with the agammaglobulinemic patients. None of the latter group developed any evidence of antibody production and none showed evidence of plasma cell proliferation after stimulation with typhoid and paratyphoid organisms.

Morphologic studies indicated that here in human subjects just as in experimental animals, antigenic stimulation induces in the bone marrow vigorous maturation of cells of the hematopoietic reticulum along the plasma cell line. In contradistinction, this maturational sequence appears to gain no impetus from antigenic stimulation in the agammaglobulinemic patient.

TABLE 21
BONE MARROW PLASMA CELLS IN AGAMMAGLOBULINEMIA

Patient	Age	Sex	Plasma cells per 5,000 nucleated marrow cells		
			Mean	Range	Number 5000 cell counts
12 Normal children	2½-15	—	19.8	11-32	12
15 Normal adults	18-41	—	31.0	8-61	15
Agammaglobulinemic Patients					
E.S., 7-year-old male	7	M	0.25	0-1	4
W.A., 7-year-old male	7	M	0.00	—	4
L.L., 26-year-old female	26	F	0.00	—	4
F.H., 58-year-old male	58	M	1.0	0-3	4

TABLE 22
COMPARISON OF PLASMA CELL RESPONSE AND ANTIBODY RESPONSE IN NORMAL PERSONS AND PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	Plasmacytes per 20,000 nucleated marrow cells		Typhoid (H) agglutinin titer	
	Before antigenic stimulation	After antigenic stimulation	Before stimulation	After stimulation
Normal children				
R.L.	104	530	no titer	1-20,480
W.O.	47	269	"	1-10,240
R.A.	72	312	"	1-10,240
K.O.	94	515	"	1-20,480
Agammaglobulinemic patients				
E.S.	1	0	no titer	no titer
W.A.	0	0	"	"
L.L.	0	2	"	"
F.H.	5	7	"	"

COMPARISON OF RESPONSE TO ANTIGENIC STIMULI OF LYMPH NODES

Prior to injection of antigenic substances, lymph nodes were removed by surgical excision from the inguinal region of 5 patients with agammaglobulinemia and from 4 normal persons. Study was made of the lymph node structure and cytology employing fixed tissue preparations stained in the usual way and imprint preparations stained with Romanowski blood stains. Abnormalities of the architecture of the lymph nodes were observed in the lymph nodes of agammaglobulinemic patients. These include: (1) relative thinness of the cortex of the node, (2) relative deficiency of primary and secondary follicles, and (3) relative abundance of fibrous tissues extending out from the hilus of the node.

In the node from one of the agammaglobulinemic patients, L. L., hyperplasia of the fixed reticulum cells and hypertrophy of the node were present as revealed by initial biopsy. Plasma cells were absent from the nodes of each of the agammaglobulinemic patients, while an occasional plasma cell was found in the node from each of the normal children prior to antigenic stimulation.

Following preliminary removal of a node, each of the 4 patients with agammaglobulinemia and each of 6 normal children were injected intradermally and subcutaneously with 1.0 cc. typhoid-paratyphoid immunizing antigen. The injection was made into the skin and subcutaneous tissue of the thigh. Four days later an inguinal lymph node draining the site of injection was removed surgically from each patient, imprinted, fixed, and stained according to the fashion previously indicated. Hypertrophy of the nodes occurred in each of the 10 subjects. In normal children the changes induced by antigenic stimulation included: (1) increase in size of the lymph nodes, (2) increased numbers and activity of germinal centers, (3) evidence of increased proliferation of lymphocytes, (4) proliferation of the cells of the fixed reticulum, (5) cytoplasmic budding of lymphocytes, and (6) significant plasma cell accumulation, especially pronounced in the medullary cords.

Morphologic evidence suggested that in these subjects plasma cells developed largely by heteroplastic metamorphosis from the reticulum of the medullary cords. Some plasma cell formation was observed in the perifollicular areas of the node as well. In contrast, the lymph nodes from patients with agammaglobulinemia who had been given comparable stimulation showed changes comparable to those observed in the normal subjects with the single exception that no plasmacellular proliferation occurred.

Similarly, but even more intensively, the lymph node changes occurring in response to a secondary injection of antigen in normal persons included abundant plasmacellular proliferation in the medullary cords and perifollicular zones. These cells again failed to develop during the secondary response of patients with agammaglobulinemia.

It is concluded from the hematologic observations that in each of 7 cases of agammaglobulinemia studied in our laboratory, evidence of profound malfunction of the reticulum was observed. The abnormalities noted are summarized in table 23.

Common to all these cases of agammaglobulinemia, then, is a deficiency of development of reticulum cells along plasmacyte lines. This phenomenon is particularly striking when the re-

TABLE 23
HEMATOLOGIC DISTURBANCES IN PATIENTS WITH AGAMMAGLOBULINEMIA

Patient	*Type of hematologic disorder observed*	*Classification of syndrome*
E.S.	Transient neutropenia, extreme leukocytosis, absence of plasma cells, failure of plasma cell development on antigenic stimulation.	"Immunologic paralysis" congenital
W.A.	Transient neutropenia on several occasions, extreme leukocytosis, absence of plasma cells, failure of plasma development on antigenic stimulation.	"Immunologic paralysis" congenital
T.A.	Persistent ? neutropenia Absence of plasma cells—failure of plasma cell development on antigenic stimulation.	"Immunologic paralysis" congenital
T.T.	Persistent extreme neutropenia; arrested development of neutrophils in bone marrow, decreased number of plasma cells.	"Immunologic paresis" congenital
F.T.	Cyclic neutropenia, arrested development of neutrophils in bone marrow, decreased number of plasma cells.	"Immunologic paresis" congenital
F.H.	Absence of eosinophils and precursors, thymoma (tumor of fixed reticulum—benign), pronounced reduction of plasma cells, failure of plasma cell development on antigenic stimulation.	"Acquired immunologic paresis"
L.L.	Generalized hyperplasia of the fixed reticulum, hemolytic anemia, absence of plasma cells, failure of plasma cell development on antigenic stimulation.	Probably acquired "immunologic paralysis"
Young's case	Lymphopenia (extreme)	?
Keiden's case	" "	?
Rohn's case	" "	?

sponse of the reticulum of these patients to antigenic stimulation is compared with that of normal children and adults. In the normal children, proliferation of plasma cells and heteroplastic maturation of the reticulum in the direction of plasma cells is the regular concomitant of the antigenic stimulation and consequent antibody production. Such is not the case in agammaglobulinemic patients. In contradistinction, failure of both antibody production and plasma cell accumulation characterize the failure of adjustment of the reticulum of the agammaglobulinemic patients to the demands of antigenic stimulation.

It is certain that the thymic tumor, the benign but intense reticular hyperplasia, complete lack of eosinophils, transient, persistent, and cyclic neutropenias turned up in the hematologic studies of our patients and the lymphopenia observed by others[22, 24, 38] might each represent diverse actions of bacterial or virus agents on the reticulum. That is to say, it is possible that the hematologic disturbances other than the plasmacytopenia may have only an indirect relationship to the agammaglobulinemia. But more attractive to us is the hypothesis that in these diverse but profound hematologic disturbances is reflected a disease of the reticulum or some organizer of reticular function which finds absolute expression in failure of gamma globulin and antibody production as well as failure of plasma cell proliferation.

REACTION OF AGAMMAGLOBULINEMIC PATIENTS TO GRAM-NEGATIVE BACTERIAL ENDOTOXINS

The intradermal injection of endotoxins in normal persons results, after a latent period of several hours, in a skin reaction characterized by erythema, edema, induration, heat, and tenderness. This reaction is seen in almost all normal subjects and doubtless is responsible for the local tenderness and soreness which accompany immunization with gram-negative microorganisms or their products. Some experimental animals, particularly rabbits, like man develop erythematous, indurated local reactions to the intradermal injection of gram-negative bacterial endotoxins. This latter skin reaction has been shown to be associated with preparation of the skin for the local Shwartzman reaction.[54, 55] Biochemical studies indicate that associated with the local reaction to endotoxin in rabbits is a pronounced enhancement of aerobic glycolysis and consequent local accumulation of lactic acid.[56] This biochemical anomaly has further been shown to be dependent, in part at least, on the availability of polymorphonuclear leukocytes.[55] The exact biologic nature of the dermal reaction to gram-negative bacterial endotoxins, however, has not been established, but its obvious similarity to the tuberculin and histoplasmin skin reactions which are prototypes of bacterial hypersensitivity have been pointed out.[57]

Gram-negative bacterial endotoxins adminis-

tered intravenously produce, with small doses, chills, fever, malaise, headache, and signs of systemic intoxication. In man, as well as in experimental animals, large doses may result in shock and death. Although much information has recently been accumulated which sheds considerable light on the nature of the local and systemic responses to endotoxins,[58-64] and their relationship to other biologic phenomena, complete understanding of these reactions is lacking. Particularly it must be stated that association or dissociation of the local and systemic reactions to gram-negative bacterial endotoxins from classical immune phenomena and from bacterial-type hypersensitivity cannot be made unequivocally on the basis of current evidence.

To investigate the nature of reactions of human hosts to parenteral administration of endotoxin as well as to gain additional information concerning the reactivity of agammaglobulinemic patients to bacterial products, preparations containing gram-negative endotoxins were injected into patients with this disease. The following observations were made: (1) agammaglobulinemic subjects, just as normal persons, develop an intense local reaction to intradermally injected gram-negative bacterial endotoxin, and (2) chills, fever, headache, general malaise, as well as other evidence of systemic intoxication occur with equal intensity in agammaglobulinemic and normal persons after the intravenous injection of products containing endotoxin.

As an example of these observations, 4 agammaglobulinemic patients and 4 normal persons were injected intradermally into the skin of the thigh with 0.2 cc. typhoid-paratyphoid immunizing antigen. (This preparation, prepared by Lederle Laboratories, Inc., contains 1,000 million typhoid organisms and 500 million paratyphoid organisms per cubic centimeter.) No immediate reaction occurred in any instance. However, approximately six hours following injection, each of the 8 subjects developed erythema which progressed during the next twenty-four hours to an intense local inflammatory reaction characterized by pronounced erythema and severe induration. This reaction was indistinguishable in its gross aspects from a strongly positive tuberculin reaction, and was no different in the agammaglobulinemic subjects from the reaction of the normal persons.

Similar, but somewhat less intense local reactions occurred in both normal and agammaglobulinemic persons after intradermal injections of 5 μg. of the partially purified polysaccharide endotoxin derived from *Pseudomonas aeruginosa* (Piromen). The results obtained are summarized in table 24.

In another experiment, the effects of intravenous administration of gram-negative bacterial endotoxins to normal and agammaglobulinemic persons was studied. As is shown in table 24, almost identical temperature responses were produced in representatives of the 2 groups.

In addition, chills, headache, and general malaise developed with the same frequency and approximately the same intensity in normal and agammaglobulinemic subjects. Purified pyrogens as well as crude vaccines resulted in this type of response in both groups of patients.

We must reason from these observations that local reactions to gram-negative bacterial endotoxin doubtlessly occur in the complete absence of circulating antibodies and probably do not in-

TABLE 24

EFFECT OF GRAM-NEGATIVE BACTERIAL ENDOTOXINS ON NORMAL AND AGAMMAGLOBULINEMIC PERSONS

	Patient	*Response to endotoxin*			
		I.D. inj. of 0.2 cc. typhoid vaccine	*I.D. inj. of 25 Microgram Piromen*	*I.V. inj. of 10,000 typhoid organisms*	*I.V. inj. of 50 Microgram Piromen*
				Maximum temp.	Maximum temp.
Agammaglobulinemia	E.S. 7-year-old male	4+ erythema 3+ induration	3+ erythema induration	103.2	102.6
	F.H. 58-year-old male	4+ erythema 4+ induration	2+ erythema induration	102.8	102.2
	L.L. 26-year-old female	4+ erythema 4+ induration	2+ erythema induration	102.6	101.8
	W.A. 7-year-old male	3+ erythema 3+ induration	2+ erythema induration	104.8	103.2
Normal	R.G. 32-year-old male	4+ erythema 4+ induration	2+ erythema 2+ induration	102.8	101.6
	J.P. 12-year-old male	4+ erythema 3+ induration	1+ erythema 1+ induration	103.2	102.4
	R.A. 7-year-old female	3+ erythema 3+ induration	2+ erythema 1+ induration	104.2	103.2
	W.O. 7-year-old male	4+ erythema 4+ induration	2+ erythema 2+ induration	105.2	102.2

volve antibodies, antigen-antibody reaction, or capacity to produce circulating antibodies in the usual sense.

Additional experiments show that refractoriness to the febrile and intoxicating effects of gram-negative bacterial endotoxin develop with equal facility in agammaglobulinemic and normal persons. The results of these studies are illustrated in figures 5 and 6 where the development of refractoriness in a normal and agammaglobulinemic patient are compared. Each of these patients was given 20,000,000 T.A.B. organisms intravenously on each of 12 successive days. As may be seen in the figures, both patients became completely refractory to the production of chills and fever by this dose of typhoid-paratyphoid vaccine. Whereas, in the normal person, the development of refractoriness to this particular vaccine is temporally associated with the appearance of agglutinins in the serum, such is not the case with the agammaglobulinemic subjects. To the contrary, refractoriness develops in the complete absence of antibody production. These data are interpreted as evidence of the dissociation of the capacity to develop refractoriness against the effects of endotoxin from the capacity to produce circulating antibodies.

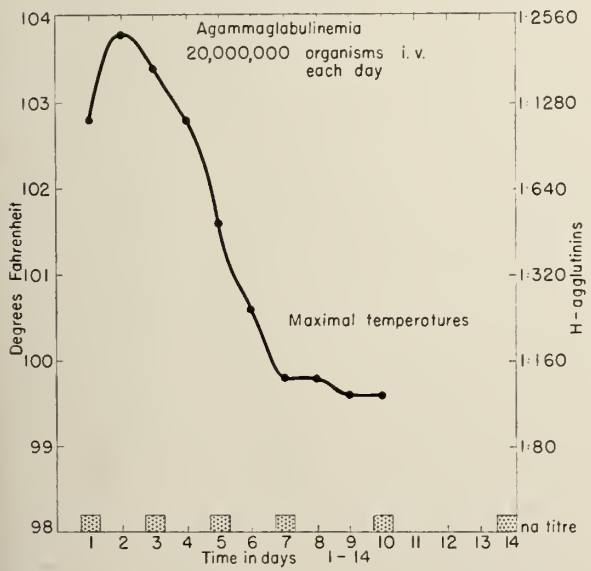

Fig. 5. Development of refractoriness to the febrile effect of typhoid vaccine upon repeated intravenous injection in patient with agammaglobulinemia. Note failure of immune response.

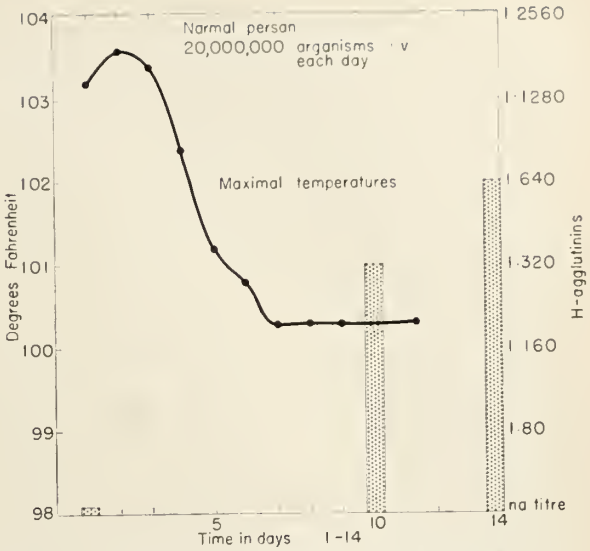

Fig. 6. Development of refractoriness to the febrile effect of typhoid vaccine upon repeated intravenous injection in normal person. Note excellent immune response.

PRODUCTION OF ACUTE PHASE REACTANTS IN PATIENTS WITH AGAMMAGLOBULINEMIA

We have also employed the agammaglobulinemic patient, our incisive experiment of nature, to gain evidence concerning the relationship between acute-phase serologic reactions and antibody production. It has been proposed on several occasions that C-reactive protein might represent a kind of natural antibody.[66, 67] In addition, evidence has been presented indicating that production of antibody is correlated with the prior appearance of C-reactive protein in the serum.[68, 69] These latter data have been interpreted as evidence that release of C-reactive protein reflects an, as yet incompletely elucidated, essential step in the formation of antibody. It was postulated that should C-reactive protein formation be an essential event in antibody production, the agammaglobulinemic patients with their immunologic paralysis might show abnormalities in production of this protein. Similar reasoning prompted study of the serum mucoprotein concentration.

The stimuli used to induce C-protein formation in normal and agammaglobulinemic subjects were intradermal, subcutaneous, and intramuscular injections of typhoid-paratyphoid vaccines and polysaccharide pyrogen from Pseudomonas (Piromen). In addition, the response to intravenous injection of each of the latter compounds was also studied. Finally, observations were made on the concentration of acute phase reactants in the serums of 5 of the agammaglobulinemic patients during the course of acute infection.

During control periods, when the patients were free of infection and had not received stimulation with bacterial products, C-reactive protein

was absent from the serum of the patients with agammaglobulinemia. After each of the stimuli listed previously, C-reactive protein appeared in the serum, the concentration being dependent on the intensity of the systemic reaction produced by the individual stimuli. The quantity of C-reactive protein produced, as estimated by the semiquantitative precipitation method of Anderson and McCarty,[70] did not differ in normal and agammaglobulinemic subjects.

Associated with the development of refractoriness to fever upon repeated intravenous injections of gram-negative bacterial endotoxins, this acute-phase protein decreased and finally disappeared from the serum even though the same amount of endotoxin was being administered each day as was the case at the time that initial injection resulted in a vigorous production or liberation of C-reactive protein.

Similarly, just as in normal subjects, agammaglobulinemic patients were shown to be capable of developing elevations in erythrocyte sedimentation rate, as well as increased concentration of serum mucoprotein as a function of acute disease or systemic response to noxious stimulation. These data suggest in contradistinction to certain speculation that C-reactive protein formation, as well as other acute-phase reactions, are probably not directly associated with antibody production. The possibility remains, however, that C-protein formation or other acute-phase phenomena reflect an early adjustment of a complex process resulting in antibody production. If this is the case, the formation of C-protein might occur while the formation or release of antibodies was blocked at a later stage in the postulated sequence of events and still be related to or essential to antibody production. Suffice for this discussion the observation that C-protein is formed in normal amounts in patients completely unable to elaborate circulating antibodies or gamma globulin who have an associated inability to develop plasma cells in response to antigenic stimulation.

PRODUCTION OF BACTERIAL-TYPE HYPERSENSITIVITY IN PATIENTS WITH AGAMMAGLOBULINEMIA

A primary objective of this investigation has been to initiate, if possible, an immune response in patients with agammaglobulinemia. One attempt to induce production of anaphylactic antibody has failed, but the experiments performed have provided stimulating information. Viable white blood cells were obtained from 1,000 cc. of blood from 2 donors, both of whom had been given 3 injections of typhoid-paratyphoid antigen. The leukocytes were separated from the red cells by standard methods involving precipitation of the latter from heparinized blood by enhancing aggregate formation through the addition of human fibrinogen to the blood. Viable leukocytes exposed only to nonwettable surfaces were then separated from the serum by gentle centrifugation, washed 3 times with physiologic saline, suspended, divided into 2 portions and injected intravenously and subcutaneously into an agammaglobulinemic subject. The leukocytes were shown to be morphologically and physiologically intact prior to injection. Preliminary skin tests with streptokinase-streptodornase revealed bacterial-type hypersensitivity in both of the donors and no reaction whatever in the agammaglobulinemic recipient prior to the injection of the white blood cells. Serologic studies performed serially prior to and after removal of blood from the donors indicated that each was showing a vigorous antibody response to typhoid-paratyphoid antigens, at the time blood was taken. Serial bleedings from the agammaglobulinemic subjects following introduction of leukocytes taken from the normal persons during a period of antibody production failed to reveal evidence of antibody production over a three-week period. In addition, stimulation with typhoid-paratyphoid antigen three weeks after injection of leukocytes failed to incite an antibody response. Quite different was the response to the streptococcal antigens for which the donors had shown bacterial-type hypersensitivity. The previously nonreactive agammaglobulinemic subjects showed an intense local reaction to the intradermal injection of streptokinase-streptodornase twenty-four hours after the white blood cell suspensions were administered. This exact experiment was repeated in its entirety on another patient with agammaglobulinemia with identical results. This patient too failed to produce circulating antibodies but did develop bacterial-type hypersensitivity after introduction of viable leukocytes derived from sensitive donors.

It does appear from this study that we have readily induced bacterial-type hypersensitivity against streptococcal products in agammaglobulinemic subjects by using technics which result regularly in the transfer of this type of hypersensitivity from sensitive donors to originally nonsensitive recipients. In contrast, the intravenous and subcutaneous injection of leukocytes derived from the blood of donors during a period of production of antibodies failed to induce the formation of circulating antibodies or the capacity to respond to antigenic stimulation with antibody formation in the patients with agammaglobulinemia.

SUCCESSFUL HOMOTRANSPLANTATION OF SKIN IN A PATIENT WITH AGAMMAGLOBULINEMIA

One of the great obstacles to medical progress in our era is the fact that homotransplantation is regularly unsuccessful. Although it has been suspected that the homotransplantation failure has an immunologic basis, proof of this hypothesis is lacking. As well conceived and properly controlled studies have replaced haphazard clinical observations, it has become apparent that in man and other mammals, orthotopic homotransplants always result in the eventual destruction and ultimate biologic replacement of the transplanted tissue. Homotransplantation of skin has been successful only between monozygotic twins in man or among individual members of highly inbred strains of experimental animals. Medawar and associates, along with others,[71–80] have provided substantial evidence for the immunologic theory of transplantation failure in experimental animals. This evidence includes data that in experimental animals:

1. The time required for rejection of homotransplants is approximately the same as that required for antibody formation.
2. The rate of transplantation rejection is a function of the dose of "antigen" supplied.
3. Circulation (blood or lymph) without a barrier to antibody or antigen is essential for the rejection of homotransplants.
4. Evidence for an anamnestic reaction toward homotransplants has been obtained.
5. Agents decreasing antibody formation prolong the survival of homotransplants.
6. Rejection of skin transplants is accompanied by the appearance in the blood of antibody against donor cells.

In the course of study of our patients with agammaglobulinemia and "immunologic paralysis," it was decided that homografting of skin should be attempted primarily for 2 reasons, namely: (1) to gain evidence on the basis for homotransplantation failure in man, and (2) as an initial step in possible replacement therapy for these patients if the deficient cells, tissues, or organs could be identified.

Consequently, the following experiment was performed. Skin taken from an agammaglobulinemic child was placed on a clean granulating surface of another unrelated child of different blood type. The recipient was a child capable of accepting autotransplants with facility. At the same time, skin taken from a 45-year-old woman of blood group A was placed on the denuded area of the 7-year-old boy with agammaglobulinemia, blood group O. In the former instance, the tattooed full-thickness graft showed a splendid initial take two weeks after application and was then rejected with complete necrosis and slough occurring within a period of one month. This is the usual fate of skin homotransplants. To the contrary, the split-thickness and full-thickness skin homograft placed on the patient with agammaglobulinemia have taken, grown, and are still surviving without showing any reaction eight months after application.

DISCUSSION

Many points presented by the observations made in the course of this investigation require discussion and elaboration. Because of the limitations in space, most of these will be left to future reports and the definitive publication of the individual observations. The purpose of this report has been to call attention to the clinical syndrome presented by patients with agammaglobulinemia, to report studies designed to elucidate the underlying mechanisms of this metabolic disorder, and to emphasize the phenomenal opportunity offered by the availability of these patients, as experiments of nature, to delve into unsolved problems in immunology.

The discovery of 8 such cases during the nine-month period that this study has been in progress, we feel to be a true reflection of the relative frequency of this syndrome. These patients undoubtedly have not been discovered clinically in the past because the disease, as we now know it, did not exist. It seems unlikely that patients with such an extreme susceptibility to bacterial infection would have survived even the first year of life in the preantibiotic era. Just one of the attacks of meningitis or pneumonia would have been sufficient to destroy most of them, and the threat to survival of the recurrent bacterial disease would have been overwhelming. These patients represent then, a true product of the antibiotic era. This statement is not meant to imply that antibiotics are responsible in any way for the development of the metabolic disorder itself, but rather that treatment of the individual infections with sulfa drugs and antibiotics has permitted survival of the patients long enough so that the clinical disease may be expressed. From the observations made up to the present time, it seems likely that many patients who suffer from recurrent severe bacterial infections have their difficulty because of immunologic handicaps, such as that responsible for the agammaglobulinemia in our patients.

The concept that agammaglobulinemia may be subdivided into congenital and acquired diseases receives vigorous support from our observations. The finding that the 6 children stud-

ied in our laboratory who have the congenital disease are all boys representing 4 families supports the proposal that the congenital form of agammaglobulinemia reflects an inborn error of metabolism transmitted as a sex-linked recessive trait. The 2 adult patients in our series, a 58-year-old male who has had clinical disease of four years' duration and a 26-year-old female who has been ill for eight years, support the concept that agammaglobulinemia may be an acquired disease which can occur in either sex at any age.

Our discovery that patients with agammaglobulinemia regularly show evidence of a disorder involving the hematopoietic reticulum provides valuable information. In the first place, this observation dictates the necessity of searching for an associated agammaglobulinemia in patients with granulocytopenia, agranulocytosis, and even cyclic neutropenia. Secondly, the information strongly suggests that reticulum cells represent a target cell in our quest for knowledge of the cellular mechanisms of antibody and gamma globulin elaboration. From these observations, the fixed and free reticulum and ultimately their plasma cell derivatives assume renewed prominence in the struggle to erect hypotheses and experiments which will lead to better understanding of the immune mechanism and provide us with its ultimate control.

More than provocative are the individual observations on the reactivity of these patients to the variety of stimuli provided. Certain it is that all of the patients with agammaglobulinemia suffer from an immunologic handicap. Of the 7 patients, 4 have been shown to be unable to produce any demonstrable circulating antibodies and to produce only extremely small amounts of antibodies and no electrophoretically demonstrable gamma globulin. It seems reasonable to conclude from these data that failure to produce gamma globulin is dependent on the same deficiency as that responsible for the failure to produce antibodies and vise versa. The corollary of this conclusion is the hypothesis that under normal circumstances, gamma globulin represents antibodies and individuals handicapped in the production of one of these compounds are similarly handicapped in the synthesis of the other. The available data support this proposition. From study of these patients, renewed respect is gained for the importance of classical immune mechanisms in the defense of the host against the occurrence and recurrence of bacterial disease.

Obviously, from these results, much needs to be learned concerning the basis of resistance to and recovery from virus infection. Clinical observations indicate that many virus infections in patients with agammaglobulinemia express themselves normally, result in ultimate recovery in the usual fashion, and do not recur in the manner that is characteristic of bacterial infections in these patients. To create a dilemma we have, in this study, demonstrated that patients with agammaglobulinemia express the same difficulty forming antibodies against viruses that they do producing antibodies against bacteria and their products. This information must be interpreted as evidence suggesting:

1. Antigen-antibody reaction in the usual sense probably does not play a role in development of the symptomatology of many virus infections.
2. Recovery from virus infections occurs in those unable to produce circulating antibodies.
3. Inhibition of recurrence of virus infection may have a basis other than or in addition to the production of circulating antibodies.
4. Minute amounts of antibodies or gamma globulin may provide a defense against virus infections.

These observations should prove provocative to the virologists in their search for means of controlling virus diseases of man and animals.

The data obtained from study of bacterial-type hypersensitivity in these patients unfortunately is equivocal, and the study does not yet permit us to either associate or dissociate the mechanisms involved in bacterial-type hypersensitivity reactions from those involved in development of anaphylactic immunity. A skin reaction was consistently developed by one of the agammaglobulinemic children after the intradermal injection of tuberculin and "purified protein derivative." However, this skin reaction, which developed in 1 of the children in whom a true immunologic paralysis was demonstrated, showed only erythema and no demonstrable induration. Indeed, although the erythema lasted between forty-eight and seventy-two hours, most observers would not accept the skin lesion produced as evidence of a positive Mantoux reaction. None of the rest of our patients were tuberculin reactors. Furthermore, tests for bacterial-type hypersensitivity to streptococcal and pneumococcal vaccines producing a high percentage of positive reactions in the general population were negative in these persons. From these data, admittedly inconclusive, we must reason that the handicap responsible for agammaglobulinemia and immunologic paralysis is associated with the demonstrated failure of these patients to develop bacterial-type hypersensitivity.

The observations recorded in this paper, how-

ever, demonstrate that reactivity to gram-negative bacterial endotoxins is similar in normal persons and in persons having agammaglobulinemia. These observations taken with others made in the course of the study indicate clearly that reactions to gram-negative bacterial endotoxin are not dependent on circulating antibodies. The observation that refractoriness to gram-negative endotoxin develops in patients unable to produce circulating antibodies serves to dissociate the development of this type of refractoriness from capacity to produce antibodies.

The relationship of host reactions produced by gram-negative endotoxin to the phenomenon of bacterial-type hypersensitivity is not clarified by these data, although it is tempting from our observations to conclude that the regular occurrence of reactivity to gram-negative endotoxins in agammaglobulinemic patients dissociates, at least to some extent, the latter phenomenon from the mechanisms responsible for development of bacterial-type hypersensitivity to streptococcal products which apparently is deficient in these patients.

From the data presented, it is certain that refractoriness against the febrile and intoxicating effects of gram-negative bacterial endotoxin in man can now be dissociated from the capacity to produce circulating antibodies. The agammaglobulinemic patients, even those possessing complete immunologic paralysis, developed refractoriness to the febrile effect of endotoxin with the same facility as did normal persons.

The observations on both the agammaglobulinemic patients and on normal persons indicate that much yet remains to be learned concerning bases of resistance to and recovery from virus infections, the relationship of anaphylactic antibody production and bacterial hypersensitivity, the true nature and mechanisms involved in the development of bacterial-type hypersensitivity, the basis for local and systemic reactions to gram-negative bacterial endotoxins, the nature of refractoriness against the systemic action of endotoxins, and the significance of and bases for acute-phase phenomena. Although observations made on the agammaglobulinemic subjects have not solved any one of these biologic problems, they have, in several instances, narrowed the avenues of approach and cleared the way for hypotheses likely to shed light on these important relationships.

Perhaps the most provocative of these many observations is that concerning the feasibility of homotransplantation in the absence of immunologic reactiveness. The observation too that agammaglobulinemia may be an acquired disease is particularly stimulating in this regard.

These 2 observations taken together provoke us to speculate that ultimate universal homotransplantation with its obvious advantages to all of medicine might gain reality through relatively simple immunologic manipulations rather than through some fantastically complicated system of tissue and organ matching. Observations on the agammaglobulinemic patients suggest possible approaches to this problem. Speculating further in this same vein, it seems probable that many of the unsolved problems of medicine might yield to methods providing even temporary control of the immune response. A few of these unsolved problems which come quickly to mind include the wastage of pregnancy due to erythroblastosis fetalis and possibly to A-B-O incompatibilities, the annoyance of allergy, the now numerous life threatening autoimmune hematologic disorders which clearly represent a misdirected immune response, and polyarteritis nodosa, lupus erythematosus, rheumatic fever, nephrosis and nephritis, any or all of which might be based on mistaken or misdirected host reaction. Intensive investigation of the provocative experiment of nature represented by the agammaglobulinemic patients could well be the incisive approach needed to permit accumulation of knowledge which would provide control of the mechanism of adjustment disturbed in these patients, which can operate deleteriously as well as beneficially for the host.

From the practical standpoint, the patients themselves present a problem demanding attention. Doubtless we can help them greatly by giving intramuscular injections of gamma globulin synthesized by intact humans and by providing prophylactic antibiotic therapy against many infections. But by doing this, we leave them with the residual handicap of immunologic unresponsiveness. A driving force in our laboratory is a desire to induce in these patients a capacity to react to antigenic material. A glimmer of light in this direction, perhaps, is the observation that skin reactivity to streptococcal products can be induced in these patients by the parenteral administration of viable white blood cells. Further experiments along this line are both in progress and are being contemplated. It is our conviction that should we discover a means of inducing antibody formation in the patient with agammaglobulinemia, our studies will not only have been of real service to him, but we also will have taken a big step toward ultimate control of immunologic phenomena. The use of prophylactic antibiotics in these patients has the distinct disadvantage of changing their bacterio-

logic flora into one consisting of ever threatening resistant microorganisms against which adequate therapy is not available.

SUMMARY

1. Descriptions of 8 patients having agammaglobulinemia are presented. These include 6 male children having the congenital disease and 2 adults with the acquired form.

2. The basic clinical problem presented by the extreme susceptibility of these patients to bacterial infection is considered.

3. Simple methods for diagnostic screening are suggested. These include measurement of the zinc turbidity reaction of the serum and titration of isohemagglutinins against heterologous blood group cells.

4. The existence of a profound immunologic handicap in each of these patients is reported. "Immunologic paralysis" was shown to be present in 4, while 3 showed evidence of minimum immunologic reactivity.

5. Profound hematologic disturbances in each of the agammaglobulinemic patients are described. These include various forms of neutropenia, eosinopenia, thymic tumor, and generalized proliferation of reticulum cells.

6. A deficiency of plasma cells in the hematopoietic tissues and failure of plasmacellular development from reticulum in response to antigenic stimuli is reported.

7. It is suggested that all of the hematologic abnormalities occurring in agammaglobulinemic patients, including lymphopenia reported by others, have a common denominator in failure of heteroplastic maturation of the reticulum.

8. Identical reactions of agammaglobulinemic patients and normal persons to parenteral injections of gram-negative bacterial endotoxins are reported.

9. Similarity of acute-phase serologic reactions in agammaglobulinemic and normal subjects is pointed out.

10. Transmission of bacterial-type hypersensitivity against streptococcal products by injection of white blood cells from streptococcal sensitive donors is reported.

11. Successful homotransplantation of skin in a patient with agammaglobulinemia is described.

12. The possible implications of these observations on immunologic theory and future approach to immunologic problems are discussed.

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Management of Abortion*

LEONARD H. BISKIND, M.D.
Cleveland, Ohio

To develop some unanimity of thought in approaching this subject, let us first define abortion. We have accepted Greenhill's[1] definition as the "term applied to the process of the expulsion of a dead or nonviable fetus," to which we have added an arbitrary time limit of the sixteenth week of pregnancy, calling all pregnancies lost between the sixteenth to twenty-eighth week, miscarriages. Premature labor is the term arbitrarily used to denote onset of labor after the twenty-eighth week.

We are aware of the voluminous literature relating to the value of hormones and other substances for use in the management of threatened abortion. By contrast, many other reports have appeared wherein patients were given no medication whatsoever, and the results were practically identical with those obtained by the investigators who were using hormones in one form or another. Actually, it has been said that less than 4 per cent of the patients could theoretically have been helped by such hormone therapy. Greenhill,[2,3] in several editorial comments in recent Year Books of Obstetrics and Gynecology, pointed out that since so many early threatened abortions result from abnormal conceptuses, there is no point in continuing any form of therapy too long. He feels that a seven-day trial is sufficient. However, he suggests that in all cases of bleeding in early pregnancy, a speculum should be gently inserted into the vagina to make sure that there is no cause, other than the pregnancy, for the bleeding. If nothing abnormal is seen through the speculum and bleeding continues from the uterus, a diagnosis of threatened abortion must be made. If the patient continues to bleed more than seven days with bed rest, in most instances nothing is gained by keeping this patient in bed any longer. Greenhill feels that she should be permitted to be up and about, because almost certainly this particular ovum is abnormal and nature will expel it anyway. Colvin and associates[4] state that if the pregnancy is less than two months' duration, the patient should be allowed to abort at home, but should be previously supplied with a pain relieving agent and an oxytocic. She should also be advised to save the fleshy products of abortion for further examination by her physician. If the pregnancy is more than two months' duration, the patient should be hospitalized because excess bleeding or the retention of the products of conception may require curettage.

A routine procedure at our hospital in handling threatened abortions which have become inevitable or incomplete has been to admit all such patients for curettage. We feel much safer in hospitalizing and curetting these patients than if we allowed them to abort at home. Even with the best of care and medication, the danger of retained secundines is present and, in the occasional case, the possibility of sepsis must also be considered.

Stallworthy[5] points out that the fundamental therapeutic principle in threatened abortion is to prevent it from becoming inevitable. The most common sign of threatened abortion is painless bleeding during the first trimester. The pregnant uterus tends to be more irritable during this period of gestation than in the latter months and contractions sufficient to dislodge the embryo can be initiated by such factors as long automobile rides, straining because of constipation, the use of purgatives, and marital relations. Stallworthy recommends the use of progesterone and advises that the patient be kept in bed for a week after bleeding has stopped. He also suggests that progesterone be continued for several weeks after symptoms have disappeared.

It is well to point out here that no method of treatment for threatened abortion has been conclusively proved superior to any other. Treatment, no matter what type, cannot be expected to change the outcome in more than a small percentage of cases. This conclusion is based upon the fact that it is normal for eggs to differ

LEONARD H. BISKIND *is chief of the division of obstetrics and gynecology, Mount Sinai Hospital, Cleveland. He is a graduate of Western Reserve University School of Medicine, 1924.*

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among themselves in endurance, viability, and capacity for growth. Good eggs survive; abnormal eggs succumb in proportion to their survival value.[6]

The change from threatened to inevitable or incomplete abortion may be judged by the degree of bleeding comparable with the usual menstrual flow, severe cramps not relieved by the use of ordinary remedies, passing of the products of conception, a patulous cervix, and/or the rupture of the amniotic sac.

The problem of the management of incomplete abortion is sufficiently understood and there appears to be unanimity of opinion in regard to most of the aspects. As we mentioned previously, the patient should be hospitalized and the uterus emptied under strict, aseptic precautions. The discretionary use of oxytocics, antibiotics, and blood is extremely important. For many years we have made it a habit to use one of the oxytocics just after dilatation and prior to curettage. Our practice is also to leave 1 or 2 sterile, plain, cervical, or prostatic tapes in the uterine canal for twenty-four hours, depending upon the extent of the pregnancy. This serves a dual purpose in stimulating the uterus to contract and, secondly, in removing any retained secundines which were overlooked with the curet. In most instances, a dull curet is used followed by a sharp one. The house staff is constantly instructed to remember that a pregnant uterus is soft and easily perforated. Unusual care must be exercised in the operative procedure.

Improvements in obstetric knowledge, skill, and technic during the past twenty-five years, particularly in prenatal care, have brought prospective mothers to labor and delivery in a far better physical condition than ever before.

Much still needs to be done in the matter of fetal salvage. Too many pregnancies are lost by way of habitual abortion in the first trimester. The administration of estrogen as outlined by Smith and associates[7] several years ago gave promise of salvaging many pregnancies that might otherwise have been lost. During the past few years, many investigators have reevaluated the efficacy of estrogen administration as a proper prophylaxis in habitual abortion. Reports in the literature[8] now express considerable doubt concerning the value of this therapy. Besides estrogens, other hormone preparations have been prescribed and the results seem to be no different than in cases in which no hormone therapy was used.

At a 400-bed general hospital with an active obstetric staff of approximately 30 physicians, a poll was taken in regard to the use of these preparations. In habitual abortion, a great majority of the obstetricians felt that the administration of estrogen was of little or no value. Our personal results in a comparatively small number of cases have been completely negative. Bed rest and the use of paregoric seem to accomplish as much as the use of estrogens. We agree with Greenhill and others who remain skeptical as to the value of stilbestrol in the treatment of habitual abortion. We admit a personal bias toward the use of any of the estrogens in high doses for any patient who has any history whatsoever of malignancy in the family.

During the past year, reports have appeared in the literature concerning the value of flavonoids for a number of conditions, including those in which bleeding plays a major role. This bleeding is thought to be due to damaged capillaries resulting from a nutritional deficiency — absence of the flavonoids in the diet. Work has been under way in a number of hospitals in the country to determine the value of these nutritional substances in the prevention and treatment of threatened and habitual abortion. Preliminary reports are encouraging.

Very few cases of infected or septic abortion are now seen. Those that come to the emergency rooms of metropolitan hospitals usually result from self-induced, neglected abortions in which pelvic peritonitis is present and gain tremendous headway before therapy can be instituted. Most of these are associated with perforation of the uterus, bladder, bowel, and surrounding organs with the development of pelvic and then generalized peritonitis.

The management of septic abortion requires hospitalization with a determination, if possible, as to the trauma involved, such as perforation and the extent of the associated peritonitis. On rare occasions, a fulminating peritonitis and septicemia, often with an associated lower nephron syndrome, leads to fatal outcome. Therapy must be directed toward combating the infection with antibiotics, assisting the renal and general circulation with blood and fluids, and other supportive measures.

Several years ago Falk and Abelow[9] pointed out that prior to 1939, infected abortion was managed by avoiding surgical procedures and by the use of oxytocics, supportive, and palliative measures. With the advent of the sulfonamides and the antibiotics, they reviewed their records of 1,000 patients with abortions from 1936 to 1937 and 1,000 similar, consecutive patients treated from 1946 to 1947. The early series showed a total mortality of 5.8 per cent in

contrast to 1.2 per cent in the later series. All patients with postabortal peritonitis in the older series died. With hysterectomy, bilateral salpingo-oophorectomy, and vaginal drainage plus the use of the antibiotics, the salvage rate was 56 per cent in the newer series. In patients given antibiotics, febrile levels were lowered and shortened. Spread of the infection beyond the uterus was prevented. In no patient of the 1946 to 1947 series did extrauterine extension develop during treatment. In patients in whom extrauterine spread had already occurred before admission, further spread was minimized.

This work of Falk and Abelow is critical because, in their expert hands, the results were excellent. We doubt whether the rest of the profession would agree with their intensely radical approach to the treatment of septic abortion. We do know that competent general surgeons look with disfavor on the surgical approach in the treatment of generalized peritonitis. It may be that Falk and Abelow operate on their patients sufficiently early to obtain the excellent results which they report.

It is not within the province of this brief paper to consider other forms of abortion, such as therapeutic abortion which requires sound medical, surgical, or psychiatric indications. It is also impossible to do more than briefly mention the high points in the management of the various forms of abortion as they have been outlined herein.

Finally, in any discussion of the management of abortion, a word or two should be said about the emotional aspect of therapy. Most women are depressed by the loss of a pregnancy. Often they take it as a reflection upon themselves and their inability to be like other women and deliver a normal child. Many women feel that if they have 1 abortion, they will have others and that their chances of having a normal, full-term pregnancy are thereby greatly diminished. These patients should be offered a simple explanation stating that, as far as statistics are concerned, 1 abortion occurs in every 3 to 5 pregnancies, that 50 per cent or more of these pregnancies had no fetus present and would never have terminated in a full-term baby, and finally (and this is extremely important) that even 1 or 2 spontaneous abortions are no indication that future pregnancies and children will be difficult to achieve.

There is also an undue apprehension among the laity that if a patient survives a threat to abort, she will give birth to a malformed infant.[10] Pregnant women should be told that *nothing could be further from the truth* and that at least 98.5 per cent of all patients who have signs of threatened abortion in early pregnancy and who carry their pregnancy to term will have normal infants.

We can be of inestimable assistance to our patients in the management of abortion if we convey to them adequate factual knowledge relative to this subject in order to avoid serious misconceptions and anxiety. Lack of knowledge magnifies preexisting apprehension, particularly when based on ignorance and superstition.

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Report on Treatment of Obstetric Rh Isoimmunization with Hapten

CLAUDE J. EHRENBERG, M.D.
Minneapolis, Minnesota

Erythroblastosis from Rh sensitization in the Rh-negative woman is estimated to occur in 1 of 26 children born to incompatible matings or approximately in 1 of 200 deliveries. The actual incidence of erythroblastosis is probably slightly higher as other antigens such as Kell, M-N-S, Kidd, Duffy, and A and B in the A-B-O system have been recognized as occasionally being causative.

In a study during 1952 of neonatal deaths in Hennepin County, 99.7 per cent of the 19,910 live births which occurred were in hospitals. The report revealed that among 258 immature and 95 full-term babies, 5 and 13 deaths resulted from hemolytic disease in the neonatal period, respectively. In addition, during the same period, 14 of 287 stillborns were judged to have died in utero of hemolytic disease. This indicates that the disease is fatal in about 20 per cent of the cases born alive and in about 30 per cent of all Rh-sensitized pregnancies, as statistically approximately 100 of the 20,197 babies born would be expected to have erythroblastosis.

The disease then does not occur frequently nor can it be considered as an alarming situation. To the obstetrician, however, faced by the parents of one or more erythroblastotic babies and to the hematologist presented with an unsolved problem, the malady becomes important and of great interest.

The interrelationships of the Rh-Hr factors in the blood have been delineated so often that a repetition would be superfluous here. Some phases of antenatal treatment, and a particularly limited experience with one treatment, are the basis of this presentation.

The early observation of Levine and his associates[1] that Rh-negative women previously transfused or injected with Rh-positive blood have a much greater incidence of first-born babies with hemolytic disease than a comparable group of women not so treated has since been well amplified. However, with the present standards of blood transfusion procedures this source of Rh sensitization is irrelevant to the future.

More recently, it has been noted and particularly emphasized by Gainey and associates[2] in 1953 that Rh-negative women subjected to various types of obstetric manipulation while pregnant with an Rh-positive fetus are more susceptible to sensitization and erythroblastotic babies in subsequent pregnancies than Rh-negative women who have not undergone such procedures. This observation should give pause to the obstetrician in this era of early operative obstetric interference before he subjects the pregnant Rh-negative or Rh-undetermined woman to instrumental, operative, or manual procedures. Beginning in early pregnancy with inevitable or incomplete abortion, it is feasible that the placental barrier damming the ingress of red blood cells of the fetus into the maternal circulation could be opened widely by curettage. Fetal erythropoiesis begins by the third week in pregnancy so that exchange from fetus to mother is possible very early. In fact, we had a 13-week-old fetus, removed by hysterotomy, in which a positive Coombs' test was already present. Later in pregnancy excessive uterine stimulation during labor has been cited as a posisble factor in forcing fetal red blood cells across the placental barrier. In the case of the necessary cesarean section – and there is now unequivocal agreement that cesarean section has no place for the per se delivery of the potentially hemolytic diseased baby – low cervical operation has been suggested with its attendant opening incision well below the placental insertion and the gentle expression of the placenta as being more desirable than the classical cesarean section which may necessitate cutting directly through the placental barrier. Manual removal of the placenta, a procedure which has become more common with the increased incidence of hospital lying-in cases, is forbidden in the Rh-negative women except under the most dire circumstances.

CLAUDE J. EHRENBERG, *a 1920 graduate of the University of Minnesota Medical School, is clinical assistant professor of obstetrics and gynecology at the University of Minnesota.*

Presented before the North Dakota Society of Obstetrics and Gynecology at Williston, North Dakota, September 17 and 18, 1954.

It seems reasonable then, until the solution of the Rh problem is more complete, to consider the preceding not merely possible but probable factors in the genesis of fetal hemolytic disease.

The modus operandi of maternal Rh or other factor immunization is far from clear, nor is its acquisition among individuals consistent either indigenously or artificially. Why one woman spontaneously develops sensitization through one pregnancy and another bears numerous children without its development is a question which may eventually be answered by the geneticist or the immunologist, but at present remains an enigma to clinicians and to even more expert examiners. Although the pattern of immunization follows a more definite trend after antecedent incompatible blood transfusion or obstetric trauma, particularly abortion, the exceptions are sufficiently frequent to cause bewilderment. An Rh-negative woman among our cases, with a homozygous husband, was transfused with her husband's blood after her third delivery and bore two more normal children before erythroblastosis appeared in her childbearing record. Her sixth and seventh pregnancies terminated in intrauterine deaths and her eighth pregnancy, during which she was treated with hapten after the seventeenth week, terminated in the birth at thirty-eight weeks of an infant with hydrops fetalis who survived four hours. Further, evidence has shown that different women vary in their ability to produce antibodies and that some women after repeated stimuli desensitize themselves. Chown[3] and others have reported births of normal Rh-positive babies from Rh-negative mothers who have previously born one or more erythroblastotic children. Also, possibly variability exists in the response of the red blood cells of different babies to the action of the maternal agglutinins. Another woman among our Rh-negative patients was found to be pregnant with twins during her fourth pregnancy. Labor was induced at the end of the thirty-ninth week because of a rapidly rising titer which had begun in the middle of the pregnancy. Dizygotic twin girls were born who weighed 6 lb. and 6 lb. 4 oz., respectively. The two placentas were approximately of the same diameter and weight and yet one twin had severe erythroblastosis and expired a few hours after an immediate exchange transfusion, while the other twin had moderate erythroblastosis and survived after a somewhat delayed exchange transfusion.

The foregoing are cited simply to mark the difficulties attendant to the evaluation of clinical statistics.

Regardless of the preceding statements, usually after an Rh-negative woman has been immunized against Rh-positive antigens, increasing degrees of erythroblastosis with successive Rh-positive pregnancies are to be anticipated; so much so in fact, that some experts in the field recommend therapeutic abortion if more pregnancies ensue after one or two hemolytic disease disasters.

Although many exceptions have been noted, the common feeling is that the concomitant onset of maternal immunization with remainingly low antibody titers will not result in hemolytic disease or only of a mild degree, while conversely severer degrees will occur when antecedent sensitization and increasing antibody titers are present. A criterion for prognosticating severe erythroblastosis described by Zelenik and associates[4,5] and which apparently has not been widely used, is a sharp rise in the antihuman globulin serum antibodies – indirect Coombs' test.

Notwithstanding the introduction of a number of methods of treatment, such as ethylene disulfonate, anhydrohydroxyprogesterone and vitamin K, methionine, cortisone and corticotropin, and Rh hapten, almost universal consensus holds that no adequate prenatal treatment is known for the Rh-immunized pregnancy.

Since the introduction of Rh hapten by Carter[6] in 1949, we have continued to use it in the antenatal treatment of women who have born previous erythroblastotic babies or who have manifested early sensitivity with subsequent rapidly rising antibody titers. Rh hapten is a crude alcohol ether extract from Rh-positive human red cells. Chemical investigation has established it as a phospholipid but little else. The hapten we have used has been prepared by Dr. J. W. Goldsmith,[7,8] using Carter's procedure with only slight modification.

Our practice is to determine the Rh status of a pregnant woman when she registers. If she is negative, an antibody titer is done on blood drawn at her next visit and repeated at the twentieth and thirtieth week unless the husband is found to be negative. If antibodies are present, titers are made more frequently. Treatment with hapten has been limited except in a few instances to only those women who have previously born erythroblastotic babies. Emphasizing again the belief that the pathogenesis of hemolytic disease begins early in pregnancy, therapy is started as early in pregnancy as is possible.

Labor is usually induced at thirty-seven to thirty-nine weeks providing the period of pregnancy is certain and the lower uterine segment and cervix are "ripe"– a procedure which is now generally acceptable. The pediatrician is notified

TABLE 1

Period of study February 1, 1947 through June 30, 1954		
Total number of women tested		2,997
Total number of women Rh negative		513 (17%)
Husbands tested		322
Husbands not tested		191
Husbands Rh positive		274
Homozygous	56 (20%)	
Heterozygous	110 (40%)	
Number indeterminate genotype	108 (40%)	
Husbands Rh negative		48 (15%)

TABLE 2

Rh-negative mothers		
Gravida	I	166
"	II	181
"	III	107
"	IV	43
"	V (or more)	16
Total		513

TABLE 3

Rh-negative pregnancies		
Total number	1,104	
Born alive	926	(twins 6 sets)
Stillborns	23	
Abortions	122	(11.4%)
Left before delivery	39	
Total	1,110	

during labor. Immediately after delivery, hemoglobin, nucleated red blood cell, and Coombs' tests are done on the baby's blood.

When Rh hapten therapy is used, 200 mg. is given weekly or biweekly and on occasions the dosage has been doubled if the antibody titer continues to rise. Results are tabulated in tables 1, 2, 3, 4, and 5.

The validity of treating such limited material statistically can rightly be questioned, but obviously the delineation of each case history is impossible. Although any conclusions drawn from so few cases may be erroneous, the results

TABLE 4

Rh immunized without treatment		
Pregnancies	33	
Abortions	3	
Number of births (1 set twins)	31	
Without erythroblastosis	7	
Erythroblastosis	24	
Lived (1 twin)	9	
Neonatal death (1 twin)	9	
Stillborn	6	
Over-all death rate		67%
Born alive death rate		50%

TABLE 5

Rh immunized with treatment (hapten)		
Pregnancies	22	
Erythroblastosis	21	(1 Rh negative anamnestic)
Lived	13	
Neonatal deaths	3	(1 anencephalic)
Stillborn	5	
Over-all death rate		38%
Born alive death rate		14%

can be noted to parallel to some extent those last reported by Carter.[9] In her last series of 57 hapten treated cases she reports 32 per cent stillbirths as compared to 24 per cent in this group and 21 per cent neonatal deaths as compared to 19 per cent in our series. However, she reports that 20 babies in her series were born with the connotation of normal, whereas only 2 of the babies from our treated mothers were free of hemolytic disease.

Before concluding, a tribute must be accorded the pediatricians for the brilliant progress they have made in handling the erythroblastotic baby; a subject which has been ably reviewed recently by Allen and Diamond,[10] Platou and associates,[11] and others.[12]

In conclusion, an inference may be drawn that hapten or some element in it may have value in the antenatal treatment of erythroblastosis and suggestion made that further chemical investigation be conducted to establish its true worth.

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Psychosomatic Problems in Obstetrics and Gynecology*

IRVING C. BERNSTEIN, M.D.
Minneapolis, Minnesota

Gynecology was among the first of the medical disciplines to deal with psychosomatic medicine. Hippocrates and Galen recognized the connection between diseases of the uterus and the emotional disturbances of women. Indeed, the term, hysteria, derived from the Greek word, hysteros, meaning womb still testifies to their acuity. As late as the end of the nineteenth century, pathologic changes in the uterus or the ovaries were still assumed to be the cause of mental or emotional disorders.[1]

Yet, not until recent years did obstetricians and gynecologists seem to be concerned with the relationship of emotional problems to the complaints of their patients. They then began to recognize that a large proportion of women seeking aid for "female trouble" are actually troubled females. Many practitioners started to accept, at least partially, the psychogenic aspects of certain definitive female disorders.

As a result of this changing attitude, three years ago an arrangement was made whereby a psychiatrist became an integral part of the staff of the department of obstetrics and gynecology at the University of Minnesota, and the association has continued to the present time. The most important goal of the association was the aim to engender in the staff and students an awareness of the emotional aspects of illness and to teach them to handle the majority of their patients' emotional problems themselves, referring only the more serious and complicated emotional problems to a psychiatrist. Another goal aimed at assisting individual physicians in gaining some understanding of their own personalities so that their patients might not be subjected to painful manipulations and unnecessary laboratory procedures occasioned by the physician's own feelings and needs. Self-understanding on the part of the physician was also expected to make referral of patients to a psychiatrist easier.

The degree of effectiveness of a particular obstetrician or gynecologist in handling emotional problems was found to depend a great deal upon his attitude toward patients with such difficulties. If each patient were treated as a sick individual and not just as a "case," results were better. In other words, if the physician was friendly, noncritical, refrained from moral judgment, and allowed the patient sufficient time to tell her story to him in her own way, anxiety was reduced and a more adequate history was obtained. This has at times resulted in elimination of unnecessary investigations and procedures.

Some of the residents became quite effective in treating relatively severe emotional problems. Under supervision of a psychiatrist, one resident was able to treat psychiatrically a patient with severe nausea and vomiting associated with radiation therapy so that she was able to finish her course of treatment. The nausea and vomiting had been so disabling that, prior to the referral to the pyschiatrist, therapy had been discontinued. Psychotherapy here consisted of helping the patient "work through" her guilt feelings which caused her to feel that her cancer was related to earlier bizarre sexual practices.

During this three-year association, a relatively large number of patients whose complaints were primarily in their "female organs" have been referred to the psychiatrist for definitive psychotherapy. In many of these referrals the time interval between the onset of the complaints and referral to a psychiatrist was quite long, and a number of unnecessary procedures had been carried out. Some of the procedures might have been avoided with earlier psychiatric consultation.

In retrospect, it is also quite clear that the psychiatrist would have obtained better results if these patients had been referred earlier for psychiatric care. On the other hand, some patients have been referred and treated relatively early with good results. In psychiatric practice, as in all branches of medicine, the earlier neces-

IRVING C. BERNSTEIN, *a 1942 graduate of the University of Minnesota Medical School, specializes in psychiatry and is on the staffs of the department of psychiatry and obstetrics and gynecology at the University of Minnesota.*

*Read at the staff meeting of the University of Minnesota hospitals, December 3, 1954.

sary treatment is instituted, the better the results.

The presenting complaints which have eventually resulted in psychiatric referral are particularly interesting since they include such ordinary obstetric or gynecologic symptoms as painful menstruation, nausea and vomiting, infertility, and leukorrhea. They may best be discussed by detailed reference to some of the more instructive patients actually treated.

DISTURBANCES IN MENSTRUATION

Menstruation is the "badge of femininity," and the badge may be worn in misery, pain, or pride, depending on the attitude of the woman.[2] The fact should be emphasized that the mere interpersonal relationship between a doctor and his patient has probably "cured" as many patients with amenorrhea as definitive surgical or medical manipulation. Many patients are seen by doctors because of amenorrhea associated with fears, depression, and anxiety, which may or may not be recognized. In many of them, after a few interviews, menstruation occurs. Apparently the most common cause of a delayed menstrual period is an emotional disorder. Haas[1] states that menstruation more than any other bodily function can be disturbed by emotional influences.

In addition to those with amenorrhea, many patients with dysmenorrhea have been treated. The neurotic woman almost always complains of dysmenorrhea, although this may not be her major complaint. There is reason to believe that the vast reservoir of the unconscious contains repressed memories of past traumatic experiences and distorted ideas about sex which may be responsible for functional dysmenorrhea. The literature contains many observations which show that dysmenorrhea yields to a particular medical, physical, or hormonal treatment. This is not conclusive evidence that the cause of the dysmenorrhea was not emotional, since there may be many reasons for the alleviation of a symptom in response to a certain kind of treatment.

The relationship of this symptom to disturbed psychosexual development is of interest. The mother is expected to explain this bodily function to her daughter, but this presupposes that the mother herself is adult emotionally and not neurotic. Unfortunately, a great number of mothers are not mature enough to accomplish this task. Explanation of the anatomy and physiology or suggested reading are not effective in relieving the teen-ager of anxiety at the time of onset of menses if up to that time the mother-daughter relationship has been poor and if the mother has handled all matters relative to sex in a "hush-hush" manner.

This early abnormal relationship apparently sets up a psychic block against acquisition of knowledge in this area and explains why textbook material taught in high school and college courses makes little advance against age-old legendary associations which result in menstruation being referred to as "The Curse" or the "Sick Time." The emotionally immature girl frequently responds to the first menstruation and subsequent periods, too, with open fear, discomfort, and disgust, since she probably has much difficulty in accepting her feminine role.

Normally, the renunciation of earlier masculine wishes is supported by identification with the mother. The normal little girl becomes reconciled to her lack of a penis and proud that she will bear children in the future like her mother, while the neurotic girl has painful menstrual periods as evidence of her unconscious rebellion against femininity.

Mrs. S, a 35-year-old married woman, was referred to a psychiatrist because of incapacitating dysmenorrhea. She was completely bedridden at least six days a month. Her family physician tried many regimens without success and referred her to a gynecologist for a hysterectomy because of the severity of her symptoms. This patient was extremely unwilling to see a psychiatrist for this "nonimaginary" symptom, but after prolonged urging by the referring gynecologist, acquiesced.

She was seen for 31 interviews in a year, during which time her dysmenorrhea improved to the point where she was no longer incapacitated each month. In these interviews, the dynamics of the case were well brought out. This patient had had severe diabetes since childhood. Her parents had emphasized to her that no one should know of this condition. This denial had been so well impressed upon her that up to the time she was seen by a psychiatrist, neither her husband nor her child had ever seen her give herself an injection of insulin.

This patient had a younger sister in whom rheumatic fever developed at an early age and who finally died in her teens of subacute bacterial endocarditis. This girl also was not allowed to talk of her illness. There were no boys in the family. The girls were encouraged in masculine pursuits. The mother, sister, and grandmother of the patient all had dysmenorrhea.

At the beginning of psychiatric treatment, the patient was unduly concerned about the onset of her 11-year-old daughter's menstrual periods. In fact, the daughter was already prepared to go to bed as soon as her periods began. As the mother improved, the daughter's concern about her menstrual periods decreased, and eventually her periods caused her no difficulty.

As mentioned previously, the patient's parents had made some unusual demands upon her which gave her the feeling of being different from other girls, and as a result her relationship with the opposite sex was disturbed. She compensated by becoming more interested in masculine pursuits. Her major accomplishment was in golf in which she became skillful.

As the patient grew older, her parents became concerned for fear she might not marry. They found an

eligible, handsome, jobless man for her, and a marriage followed. The patient had always felt unattractive in comparison to him and deeply despised him for his lack of accomplishments and dependence on her family. He acted out the feminine role of the family. For example, he expected his wife to cut the grass, shovel the walks, and, in general, to lead him.

As would be expected, the patient was frigid, which added to her feeling of inferiority. After a few years of marriage, a pregnancy occurred and was complicated by the fact that a tubal ligation was done at the time of cesarean section. As psychiatric treatment progressed, the patient became more feminine in action and more demanding of her husband which upset him greatly. As treatment progressed, the marriage became more and more insecure, so therapy was terminated.

LEUKORRHEA

Leukorrhea at times results in psychiatric referral and has interesting psychiatric facets. Masturbation or masturbation fantasies may initiate the discharge which easily may become secondarily infected. Pelvic hyperemia caused by unreleased tension in patients with frigidity may be another underlying psychologic cause for intermittent or persistent vaginal discharge.[3] This symptom obviously annoys the fastidious person.

Mrs. T, a 25-year-old married female, was seen for 50 interviews over an eighteen-month period because of a severe vaginal discharge which had been refractory to many years of out- and inpatient care. In addition, the patient had undergone a thyroidectomy which, in retrospect, had been performed because of anxiety symptoms. In this patient, as is often the case, a major problem for the psychiatrist to overcome was the resistance to being referred to a psychiatrist. The patient objected to being sent to a psychiatrist "when I have something physical."

In this particular patient, it soon became apparent that an underlying problem was her concern about venereal disease and masturbation. The patient remembered being afraid of falling asleep as a child. "I was afraid I might put something in my vagina." Because of this symptom, she was seen by many doctors for intractable insomnia.

The fact was apparent that this patient had been preoccupied since childhood with her genital region. This preoccupation may have caused some additional secretion or may have rendered her abnormally sensitive to a normal amount of secretion. She had been told by her husband, at a time when he wished to torment her, that she probably had contracted a venereal disease from him, which indicated to her that her husband had rejected her for another woman. He later said, "I did this to protect you if the doctor said you had a venereal disease," which, of course, indicated to the patient that her husband thought she was unfaithful.

As treatment progressed, the patient's guilt feelings regarding masturbation were "worked through." In addition, she had rigid concepts about cleanliness and orderliness and had a drive to control her environment. These attitudes indicated that she had a severe obsessive-compulsive neurosis, which was her basic problem.

The patient's concerns and difficulties relative to her vaginal discharge fluctuated during the period of psychiatric treatment. Psychotherapy definitely influenced her concern about her vaginal discharge and probably influenced its quantity. The concern about vaginal discharge itself is a major problem in the treatment of leukorrhea. When psychiatric treatment was terminated, the patient no longer required gynecologic care.

Another patient was seen with the same presenting complaint. In this patient, the same overconcern about cleanliness existed but, in addition, "projection" was present. "People are smelling me." The patient was obviously psychotic and had been for several months. The history brought out the fact that both her mother and her husband were severe alcoholics. She never received attention from them except when she complained of her discharge, which, incidentally, served the purpose of keeping the husband away sexually. This is a clear example of how neurotic symptoms are utilized for a patient's emotional adjustments.

The patient masturbated considerably, which was one of the few ways she received any emotional satisfaction from life. This habit contributed to the symptoms and also gave her a feeling of guilt. After psychiatric evaluation, the patient's family doctor was made aware of her emotional illness and advised to treat her regularly on a symptomatic level with a minimum of manipulation of the sexual organs. Inpatient psychiatric care was not deemed necessary because she was making a borderline social adjustment. Under this type of management, the patient has become less concerned with her vaginal discharge and her social relationships have improved.

PREGNANCY

The close relationship between pregnancy and the patient's emotions is accepted by most physicians practicing obstetrics. The wish for pregnancy and motherhood is a normal and appropriate desire in the course of feminine development. The wish, however, is present in the female psyche long before she is physiologically and socially capable of fulfilling her desires.

Pregnancy fantasies fill the psychic life of many girls from their early childhood and play an important role in shaping their attitudes toward pregnancy. The fantasies contain not only the wish for pregnancy, but they also have components of fear of pregnancy. These conflicting elements may manifest themselves alternately.

The fact that adult women in general wish children is understood, but the observation that some feelings of rejection regarding pregnancy are observed in all pregnant women is not so well known.[4] Yet, this should be expected, since pregnancy restricts a woman's activities, interferes with the pursuit of her personal life, and threatens her existence. These feelings of rejection should be kept in mind and managed by the obstetrician as he follows his patient through her pregnancy.

Nausea and vomiting of pregnancy are particularly common complaints and are experienced by more than half of all pregnant women. The condition is felt to be the result of the manner in which the patient handles her feelings of

rejection.[5] The organic treatments that are reported in the literature are assumed to be effective because of their "suggestive" effects. Even those authors who feel there is a toxic etiology for nausea and vomiting of pregnancy agree with this. For example, Beck,[6] who emphatically believes in a basic toxic etiology, states that "suggestion should be liberally and seriously added to all measures."

In this department, nausea and vomiting of pregnancy are treated primarily by the utilization and application of psychiatric principles. The aim is to get the patient quickly into equilibrium psychically and organically. This is a practical consideration since the disturbance can endanger the life of the mother and child, and, moreover, the symptom is associated with a self-limiting condition — pregnancy.

If the usual symptomatic treatment, consisting of management by a sympathetic, understanding physician and routine hospitalization is not successful, the psychiatrist is called for consultation. He attempts to bring into consciousness the superficial conflict. The aim is not basic personality change, but symptomatic relief. Psychiatric treatment is therefore centered about the superficial conflict. After this has been "worked through" with the patient, the obstetrician is advised as to subsequent care of the patient. In most cases, this method of management has been successful and has greatly reduced the hospital stay of patients.

The superficial conflict usually is related to the patient's feelings about one or more of the following: (1) her pregnancy, (2) her husband, (3) her doctor, and (4) her parents.

The conflict in one patient centered about her resentment toward her husband for his insisting that she remain home to care for their dangerous dog. After a single interview, the patient discussed the situation with her husband, the dog was disposed of, and the patient recovered. In another patient, the problem was the patient's resentment toward her father because of her fear of what he would do when he became aware of her pregnancy. This symptom was an overlay to a basic oedipal conflict. In yet another patient, the symptom was related to the patient's resentment toward her doctor for being so rigid with her.

These three patients had no further incapacitating nausea and vomiting after the single interview. In another case, the conflict was related to the husband, but so complicated that the patient recovered only enough to go through twelve days at home after psychiatric treatment was instituted. The results in this last instance were poor but are not an indication that the problem was organic, but rather that the conflict was more deep-seated than usual.

STERILITY.

That sterility and its implications result in psychiatric referral should not be surprising because, if a pregnancy is desired and does not occur, the individuals concerned will be emotionally upset regardless of the underlying reason for wishing a child — whether it be genuine motherliness, competition with the environment, or overcompensation for rejection of the feminine role. An overtly expressed wish for a child is not necessarily proof of true motherliness.

The masculine woman may be unduly preoccupied with the desire to become pregnant as overcompensation for her masculinity. She may wish to prove that she is able to fulfill her biologic function. If she does not become pregnant easily, this type of woman tries to reach her goal with the greatest tenacity. She subjects herself to all kinds of examinations and treatments, frequently changes physicians, and never is reconciled to her sterility. Neither is she able to accept other ways of satisfying her desire for motherhood.

In usual cases of sterility, the feminine motherly woman gratifies her wish for motherhood in her love for her husband, or adjusts happily to the adoption of a child. In the masculine woman, if pregnancy occurs in spite of the conflicting inner situation, its course and delivery as well as the attitude toward the child will all reflect the mother's personality.

A patient with sterility was recently referred by a gynecologist because he felt the patient was unduly depressed because of her inability to become pregnant. The patient had always been an overly conscientious, excessively clean, meticulous, and conforming person. She always did exactly what was expected of her. She kept her husband always near her for if he was not near, she was obsessed by fears of his death. Referral to a psychiatrist was difficult because of her fears of "what would my friends think." Therapy was directed toward bringing into the patient's consciousness the fact that she was depressed because of her inability to "keep up with the Joneses," not just that she was unable to conceive. Her depression disappeared with psychotherapy.

Another patient was referred for psychiatric evaluation at her own request after an infertility work-up failed to reveal an organic cause for failure to conceive. In the first interview, the patient admitted she really did not want a preg-

nancy but "felt" that her daughter should have a sibling. As therapy progressed, the desire for pregnancy became less of a problem to the patient and treatment was directed toward helping her handle her guilt feelings about adolescent sexual activity. Finally, she was able to admit that she really did not wish a pregnancy and her concerns over her sterility vanished.

Since most physicians, including psychiatrists who treat infertility, report moderate success regardless of whether they use relatively simple methods such as sedation, vacations, hormones, weekly interviews, or complex methods such as psychoanalysis or semen implantation, the possibility must be considered that all the methods are efficacious because of their emotional significance. Any of these procedures might reduce the patient's emotional tension as well as release tubal spasm which is known to be more prevalent in tense individuals as Rubin[7] has demonstrated conclusively. Deutsch[8] believes that the physical treatment used by gynecologists to treat sterility may actually unconsciously be interpreted as punishment, and that this is the factor which is often responsible for the beneficial results obtained. She feels that expiation of old guilt feelings through suffering and sacrifice sometimes relieves "inner tensions."

PAIN

Abdominal pain and discomfort and other vague associated symptoms such as dizziness, weakness, and the like result in referral to the gynecologic service. In a certain proportion of cases, a thorough investigation reveals no organic pathology, and subsequent referral of the patient to a psychiatrist results in a diagnosis of hypochondriasis. Previously, the patient was interviewed after the investigation was completed, advised that nothing physical was found, and was discharged from the hospital. With these facts, the doctor in charge felt satisfied and relieved, but the patient was even more miserable than when first seen because her hopes for relief had been destroyed again.

These patients are now treated differently. Since most of them are from outlying communities, the recommended treatments are best carried out by the referring physicians. These physicians are advised that the symptoms of confirmed hypochondriacs are absolutely necessary for their emotional adjustment and that the patients should be managed on a long-term basis with regularly scheduled visits.

The doctor is advised (1) to listen to the recital of symptoms and not make any diagnosis, prognosis, or promises, (2) to prescribe symptomatic medications which are not dangerous, and (3) to obtain laboratory procedures and x-rays only when they are absolutely indicated. If the referring doctor can carry out these suggestions, the patient usually shows some improvement, is less of a problem to her associates, and requires less hospitalization.

A number of hypochondriac patients have been treated successfully by the referring physicians with the assistance of members of the gynecologic staff for as long as two years with gratifying results.

Mrs. W is an example of this type of patient, who was referred to the gynecologic service with the presenting symptoms of pain, diarrhea, headache, and weakness. The referring physician sent a 5-page, single-spaced, typewritten letter with the patient describing the investigative and surgical procedures which had been conducted on the patient in the preceding eleven years. Among the many diagnoses considered were amebiasis, endometriosis, leukemia, porphyria, and nervous collapse. She had undergone 3 submucous resections, a cauterization of the cervix, 3 curettements, multiple proctoscopies, and 2 laparotomies. She did not experience any prolonged improvement after any of the surgical procedures nor did she respond to any of the various medical regimens prescribed, which included utilization of various hormones, barbiturates, and narcotics.

On admission, the patient appeared ill and depressed. Diagnostic studies were again normal. She was then seen by the psychiatrist who diagnosed her as a hypochondriac and recommended that she be treated with sympathetic understanding in a manner which did not threaten removal of her symptoms. With this type of management, her general condtion and depression improved. She was discharged from the hospital in five days. Her referring physician was advised as to further care.

With regular visits to her local physicians and rare visits to the gynecologist, the patient has not been medically incapacitated for two years as she was during the preceding eleven years. Now she appears able to accept her limitations without having to develop such intense symptoms. The severe incapacitating symptoms were utilized unconsciously as excuses for her inability to attain the goals she had set for herself.

ITCHING

Itching is a symptom which is thought by most psychiatrists to have its origin in repressed hostility. Some individuals may be incapable of expressing their resentment except inwardly.

The case of Mrs. H., a 31-year-old married woman, demonstrates this fact well. She was referred by a gynecologist to whom she had been sent because of pruritus vulvae. At this point, surgery was being considered for her symptom. This patient was unlike most of the others who have been discussed in that she appeared quite eager to see a psychiatrist. In two interviews which were conducted on successive days, a great amount of information was brought forth. During these interviews, she abreacted strongly, especially when discussing how hostile she felt toward her parents and husband.

The patient was born and reared in a small town in North Dakota. Her parents were extremely strict with

her, overly religious and, at times, actually brutal for tiny infractions of rules, which resulted in her being a very docile child. She received no sex education and, among other things, no preparation for menstruation.

Early in her life she got the idea that sex was "bad" and "dirty." She learned about the menses from her sister who was two years older, and her immediate reaction was "this will never happen to me."

She had severe dysmenorrhea from the onset of the menarche. She did well in school, poorly socially, and did not date until 18 years of age. On her first date her boy friend touched her genitals. The patient became extremely frightened and guilt-laden. She was unable to study and unable to talk this situation over with anybody. She examined herself carefully, noted a small amount of secretion and itching, and became more frightened than ever. As a result of seeing an advertisement in a local paper, she finally consulted a "woman specialist" who was a charlatan. He told her she had an "infection" and gave her "internal treatment." She was now even more sure than before that she had contracted a venereal disease. After this experience, she became more frightened of men and felt guiltier than ever.

After suffering for months with the itching, she told her sister of her experience. Her sister, who was a nurse, referred her to a physician and she recovered. Thereafter, from time to time she requested physical examinations and each time asked casually about her "blood" and always received a statement that "it was all right." She never felt relieved since she was never assured that she did not have a venereal disease nor did she have an opportunity to talk of her guilt feelings. The patient married at the age of 25. The marriage and sexual relationships were unsatisfactory. On many occasions she avoided intercourse by complaining of her vulvar itching. Her husband stayed away progressively longer on his business trips. While he was gone, the patient's vulvar symptoms were intensified and she scratched more than before. She consulted many physicians because of her vulvar symptoms and sterility. The thought uppermost in her mind was that both her itching and sterility were caused by a venereal disease contracted on her first date.

The physicians she visited apparently did not recognize the psychogenicity of her vulvar itching and treated it symptomatically with little success. She was treated over a period of years with various salves, injections, and x-rays. Eventually, severe anatomic changes in the vulvar area were noted, and the patient was referred to this hospital for further study of the vulvitis which now resembled the leukoplakia of an aged person. Upon arrival, she was discouraged and fearful of cancer.

At the initial psychiatric interview, the first question she asked was whether or not she had a venereal disease. She was assured that she did not. From this time on, she discussed her feelings which have already been summarized. After these interviews she went home without symptoms. Relationship with her husband became more pleasant. She became pregnant and eventually delivered a normal baby uneventfully.

This case is unusual, of course, but demonstrates what can be accomplished with the recognition and treatment of emotional disturbances. A follow-up of this patient was obtained a few weeks ago from the referring physician. The patient did not experience vulvar itching for an eighteen-month-period after her treatment at the University Hospital. The symptom returned following her discovery that her husband was being unfaithful to her. The original referring physician now feels he himself may be able to help her "handle" her present emotional upset with its concomitant itching.

CONCLUSION

Most emotional problems encountered by the obstetrician, gynecologist, or general practitioner can be handled successfully if physicians recognize them and utilize some principles of psychotherapy. This means manipulating the relationship between the patient and doctor to improve the understanding and attitude of the patient toward herself, her illness, and her environment. This presupposes (1) that the physician has enough understanding of his own dislikes, biases, and shortcomings to be able to discount and rise above them when dealing with patients; (2) that he can listen to a patient's complaints in such a manner as to reduce her anxiety; (3) that he can give sympathetic understanding and kindly reassurance when indicated, and (4) that he can conduct his examinations in a manner that will not incur iatrogenic complications. The emotional problems which a physician recognizes are beyond his scope should be referred early to a psychiatrist.

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Lancet Editorial

False Fears of Pregnancy

A GLANCE at the articles in this issue of THE JOURNAL-LANCET shows a range of obstetric problems which are being given careful scientific thought and study. Intelligent medical observation and thought have cut greatly into the once high morbidity and mortality rates of both the mother and infant. The present rather remarkably low rates will continue to be slashed, not unlike the once mythical four-minute mile.

But perhaps now it would be wise to ask that a greater effort be exerted to enlighten our nonmedical population. Far too many half truths and old wives' tales persist, not only among those who did not finish elementary school, but among college graduates.

I remember a graduate nurse who came to me in tears because her mother had convinced her that her baby would be "marked" as the result of the fact she had witnessed a fire which destroyed a chicken house on her farm. This wasn't twenty years ago, it was 1954.

A chiropractor in the Middlewest is doing a land-office business giving treatments guaranteed to "cut labor in half." A remarkable gimmick; how to argue that a twelve-hour labor would not have been a twenty-four-hour one, or a twenty-four-hour affair a forty-eight-hour labor?

And, in 1955, I delivered a teen-age primipara who informed me that "they (her family) wanted me to have it at home. Grandmother would have come over and delivered me." The "have-it-at-home" urge seems to be springing up paralleling the "do-it-yourself" craze, but there is a limit.

Part of this desire for home deliveries can be traced to the cost of hospital care. But even if the nervous husband is a whiz at boiling water and grandmother mixes a potent hot toddy, there is no substitute for hospitalization when the unexpected inversion of the uterus occurs or when the lacerated cervix that bleeds profusely suddenly complicates the picture.

Blood and blood substitutes are readily available in even the smaller hospitals, as are sterile instruments and adequate light. These three factors are reason enough for hospitalization.

We need not give the layman a complete course in obstetrics, but let us attempt to dispel false notions during prenatal visits. The prenatal visit accomplishes many things, one of which is simply learning to know the patient, and the patient becoming well enough acquainted with her doctor to bring up some of the things about which well-meaning friends and relatives have "informed" the mother-to-be. Recently I saw a young primipara who was so terrified she could scarcely talk. After a few years of marital life she had become pregnant. Her mother had told her when she was a child that she was a "bleeder," and that if she ever became pregnant she would bleed to death. Blood studies were entirely normal, but such findings were of little comfort. Only when asked how her menstrual periods had been since her menarche could she smile again. She had always had normal, regular periods and had never bled heavily. She realized herself that if she had been the bleeder her mother claimed her to be, this would not be true; but all her fertile years had been spent with a dread of some day becoming pregnant.

As the physician learns in a scientific and factual way, let him be quick and eager to teach in understandable language those about him. Let us not complicate the uncompilcated, but let us try now to lower even more the infant and maternal morbidity and mortality by exploding old myths concerning childbirth and preventing new myths from arising.

PHILO H. ROCKWOOD, M.D.

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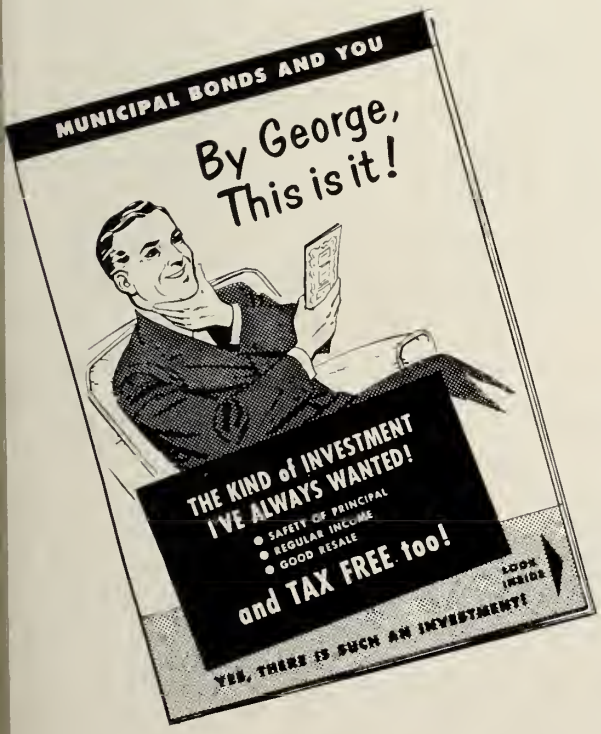

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BOOK REVIEWS

Diseases of Women, by Robert James Crossen, 1953. St. Louis: C. V. Mosby Co. $18.50.

This classic in the field of gynecologic literature was last revised in 1941. Since that time great strides have been made in the complex picture of endocrinology and hormone activity. This subject has been nicely covered with the help of Dr. Willard Allen.

Recent methods of early cancer detection are incorporated and such recent therapeutic attacks on carcinoma of the cervix as radioactive gold are mentioned. Where more than one view is held on vital subjects, such as radiation versus the operative treatment of such carcinomas, both viewpoints are carefully covered.

More attention is afforded the psychosomatic aspect of gynecology than previously was recorded, even reporting successful use of hypnosis in such age old problems as dysmenorrhea.

As previously, *Diseases of Women* is a volume for repeated reference by the general practitioner anxious to practice adequate intelligent gynecology, or for the specialist desiring a comprehensive and up-to-date coverage in the field of gynecology.

Philo H. Rockwood, M.D.

Childbirth Without Fear. The Principles and Practice of Natural Childbirth, by Grantly Dick Read, M.D., 1953. New York City: Harper and Brothers. 298 pages. $3.00.

This is a new revised and an enlarged edition of a book which has had a great influence in this country and in England. Doubtless Read's idea is a good one. Many women receive much information concerning possible dangers of childbirth, or of the chance of losing a child with an Rh difficulty, and become so frightened that they approach pregnancy with fear.

The first 97 pages of this book deal with the problems of combating fear. Latter parts of the book deal with such problems as diet in pregnancy, the phenomena of labor, the relief of pain, the use of hypnosis, the conduct of labor, breast feeding, the husband's problems, and antenatal care.

The book was written primarily for patients, but the wise obstetrician should read it, because he may gain a number of good ideas to help him handle worrisome patients.

Walter C. Alvarez, M.D.

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Cystic Fibrosis of the Pancreas in Infants and Children, by Charles D. May, M.D., 1954. Springfield, Illinois: Charles C Thomas. 93 pages. $3.00.

This concise monograph summarizes the collective thinking of the author and Dr. Charles U. Lowe on the disease which Dr. May prefers to call "cystic fibrosis of the panereas." With economy of words and directness of approach, the over-all problem is described in logical compartmentalization. A full discussion of the cause and pathogenesis of the disease is presented at the end of the work, which treats fairly the concepts of Baggenstoss, and Wolbaeh and Farber, and leaves the reader with a refreshed basis for further penetrating the mysteries of the illness.

There is a rich bibliography of 83 references. The book is to be recommended for general practitioners as well as pediatricians.

W. D. Bevis, M.D.

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NEW MEMBERS

We welcome a new member whose application has been approved by the Executive Committee:

Teachers College of Connecticut, New Britain, Connecticut. Representatives: Miss Geneva Kehr, M.A., chairman, department of health and physical education for women; and Harrison J. Kaiser, M.A., chairman, department of health and physical education for men.

PERSONNEL

Notice has been received of the death on February 16 of Dr. Joseph H. Gamet. Dr. Gamet had been director of the student health service at Iowa State Teachers College, Cedar Falls, Iowa.

Montana State University, Missoula, Montana, is seeking a director for its student heatlh service. Dr. John Scott, the present director, has resigned, effective June 30, 1955. There is a student body of 2,400 at Montana State and a staff of 5 nurses is maintained at health service. A new building is being completed for health service and is expected to be ready for occupancy in the fall of 1955.

B. W. Lafene, M.D., director of student health service at Kansas State College, Manhattan, Kansas, announces an opening for a staff physician as of September 1, 1955.

C. G. Menzies, M.D., director of health service at Michigan State College, East Lansing, Michigan, announces that Dr. Clarence J. Poppen joined the staff on January 1, 1955. Michigan State is expanding health service facilities with a $2,000,000 grant from the state and hopes to get under construction within the next few months. There is another vacancy on the staff at Michigan State and Dr. Menzies would like to hear from any interested physicians.

EXPANSION PLANS

The board of regents of the University of Nebraska, Lincoln, Nebraska, has recently approved construction of a new student health center. S. I. Fuenning, M.D., is director of university health services.

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Medical Ophthalmoscopy*

JOHN P. WENDLAND, M.D.
Minneapolis, Minnesota

THE title of this paper includes those fundus conditions which are manifestations of disease remote from the eye. This disease may be a generalized disease affecting the entire body, for example, hypertension; or primarily one organ, for example, brain tumor. The reflection of systemic disease in the eye is of great value in the diagnosis and prognosis of general disease. At times the eye manifestations may be the most prominent feature of the disease and outweigh in importance manifestations elsewhere in the body.

Under these circumstances, the eye disease not only may be useful in diagnosis and prognosis of the disease remote from the eye but actually may dictate, because of threatened blindness, what the general treatment must be. For these reasons, all who practice medicine should be interested in disease of the fundus of the eye.

NORMAL VARIATIONS IN THE FUNDUS WHICH MAY BE CONFUSED WITH DISEASE PROCESSES

It would seem apropos before discussing actual organic disease of the fundus to list a few pitfalls in the diagnosis of disease of the fundus. These pitfalls concern normal variations. In some cases the shading between the normal and the abnormal is gradual so that there is no sharp dividing line. In these cases the fundus findings may be equivocal and every clue available must be used in interpreting the fundus findings. For example, there is no sharp dividing line between a normal disk and a disk with papilledema. Many normal disks have blurred margins. Some even have elevation of the vessels as they emerge from the disk; the vessels may be seen to hump forward into the vitreous. Clues which must be used to differentiate a normal disk from that with papilledema are as follows. A normal disk often shows venous pulsation on the disk; a true papilledema rarely shows venous pulsation. A normal disk with blurred margins often appears as a small disk; this type is found in the hyperopic eye and the refraction measured with the ophthalmoscope is important. A disk with papilledema may or may not be found in a hyperopic eye. Hemorrhages are, of course, never found in the surrounding retina in a disk which has normally blurred margins. Venous congestion is not found in a disk with normally blurred margins but is always present in early papilledema. However, this sign may be unreliable as the normal disk which is most likely to have blurred margins – hyperopic eye – is also the most prone to have congenitally tortuous veins. Congenitally tortuous veins are easily confused with veins having pathologic tortuosity and congestion.

A variation in the disk which must not be confused with true optic atrophy is the temporal

JOHN P. WENDLAND, *a 1941 graduate of the University of Nebraska College of Medicine, is assistant professor of ophthalmology at the University of Minnesota and consultant in ophthalmology at the University of Minnesota Health Service and Veterans' Administration Hospital, Minneapolis.*

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pallor of myopia. Here again the state of refraction of the eye is of prime importance in the diagnosis. Most myopes of 3 diopters and over show this pallor. Some eyes which are not even myopic may show temporal pallor. These eyes all retain a normal pink color nasally in the disk, however. If both eyes of a patient are of similar refractive error, careful comparison of the 2 disks is of considerable help in diagnosing early unilateral optic atrophy. The function of the eye, visual acuity and fields, is, of course, also of great help. A deep physiologic cup in which the lamina cribrosa is plainly visible may be confused with a primary optic atrophy or a glaucomatous cup. However, a pink rim always remains in the normal cup.

Great difficulties in diagnosis also present themselves when examining a newborn fundus. The normal newborn fundus has a very pale disk, a granular macula, and a somewhat grayish periphery in which pigment clumps may be located. Caution is required in diagnosing optic disk disease or macular pathology in the newborn. The child's fundus does not resemble the adult fundus until about 2 years of age.

Myelinated nerve fibers, a normal variation, may be confused with exudates in the fundus. Myelinated nerve fibers have a more glossy surface than an exudate, and on very close inspection fine feathery edges can be observed. This feathery edge represents the actual uneven extension of the myelin sheaths of the nerve fibers in the retina. Myelinated nerve fibers occur most often at the edge of the disk but may be seen anywhere in the fundus as an isolated patch.

DISEASE CONDITIONS PRIMARILY AFFECTING THE OPTIC DISK

Papilledema. By the term papilledema we refer to a noninflammatory swelling of the optic disk. Papilledema may be caused by many different conditions. Some of the more prominent causes are brain tumor, brain abscess, subdural hematoma, arteriovenous fistula of the cavernous sinus, encephalitis, meningitis, severe anemias, polycythemia, obstruction of the central retinal vein, hypertension, orbital tumors, cavernous sinus thrombosis, lead poisoning, and ocular hypotony. Admittedly this list is incomplete, as the causes of papilledema are legion.

We have already discussed the differentiation of early papilledema from the normal disk with somewhat blurred margins. Full-blown papilledema is familiar to all and need not be described here. This condition may, however, be confused with the disk of an optic neuritis. Helpful differential points are as follows:

1. The loss of vision is usually gradual in papilledema and sudden in optic neuritis. For the same degree of swelling of the disk, the patient with optic neuritis presents much more visual loss than the patient with papilledema.

2. The swelling of the disk in papilledema may result in greater elevation than the swelling from an optic neuritis.

The papilledema of brain tumor is also important to differentiate from that due to central retinal vein occlusion or malignant hypertension. In a complete central vein occlusion no problem arises in the differential diagnosis. The fundus is splashed with hemorrhages throughout its entirety and the veins are tremendously distended. In many areas, of course, the veins are partially obscured by the extensive hemorrhages. However, the picture in partial central vein occlusion, which is not a rare condition, may mimic closely the papilledema of increased intracranial pressure. Blurring of the disk margin, loss of venous pulsation, and congestion of the retinal vessels are present. The key to the differential diagnosis lies first in the fact that partial central venous occlusion is usually unilateral; papilledema from increased intracranial pressure is usually bilateral. Second, the distribution of hemorrhages is different in both conditions. In partial central venous occlusion, the hemorrhages are present not only in the vicinity of the disk but also far into the periphery. In papilledema, from increased intracranial pressure, the hemorrhages are usually only around the disk or at least in the posterior pole of the fundus except in unusually severe cases, and even then concentration of pathology is in the disk region.

This question sometimes arises — does the patient with hypertension have a brain tumor or is the patient's papilledema the result of the hypertension? The papilledema of malignant hypertension is differentiated from that of brain tumor not by looking at the papilledema but by looking at the retinal arterioles. If the retinal arterioles have severe hypertensive changes as evidenced by pronounced generalized and focal narrowing and if cotton-wool patches and hemorrhages are present remote from the disk, probably there is no need to look further for the cause of the papilledema. The arterioles in these cases are thread-like or show pronounced focal narrowings, grade II to III. Considerable blurring of the disk margin can be present in hypertension without increased intracranial pressure, but, when the disk mushrooms forward, increased intracranial pressure is probably present.

Although papilledema does not result in the sudden loss of vision that occurs in optic neuritis,

it is still a serious threat to vision and a long-standing papilledema may result in blindness.

Optic neuritis. This condition is an inflammatory process affecting the optic nerve. The etiology of this disease is even more diverse than that of papilledema. Listed among its more common causes are multiple sclerosis and other demyelinating diseases such as Devic's and Schilder's diseases, virus infections in which the etiology is suspected but not usually proved, anemia, syphilis, thyroid disease in which the mechanism is unknown, temporal arteritis, Leber's disease, uveitis; and various toxic substances such as lead, carbon tetrachloride, quinine, methyl alcohol, and tryparsamide. We must remember that other chemicals may also give rise to an optic neuritis. Ethyl alcohol when consumed in large quantities, especially if combined with heavy smoking, may cause a gradual loss of vision and the condition known as tobacco-alcohol amblyopia. Diabetics seem prone to the development of an optic neuritis, but the cause is unknown and may not be part of the picture of diabetes.

Optic neuritis is found more often in acute anemia after hemorrhage from the gastrointestinal tract or uterus than in chronic anemia. This condition is probably the result of spasm of the vessels of the optic nerve, the spasm being carried to the point of actual occlusion of some of the vessels.

The clinical picture of optic neuritis in the early stages may vary from a normal appearing disk to a disk resembling a papilledema. In the later stages, if full recovery does not occur, the disk always shows atrophy. This atrophy varies with the severity of the damage. In those early cases with normal disks, it is indeed a disease in which neither the physician nor the patient can see anything. The doctor observes no pathology; the patient's vision is severely reduced. The etiologies listed may cause various types of field defects, and it is beyond the scope of this paper to discuss all possible causes of optic neuritis. However, I would like to single out temporal arteritis as a cause of optic neuritis for very brief discussion. This is a condition seen in elderly people between 55 and 80 years of age. Females outnumber males 3 to 1.[1] Optic neuritis or occlusion of the central retinal artery occurs in about one-third of the cases and is important from the standpoint of diagnosis and also because of the danger to vision. In about one-third of the cases in which the eyes are affected, the condition attacks both eyes. The prognosis for vision is poor when the eyes are involved. Cortisone therapy should be tried because of the danger to vision which exists, but only with time will we be able to estimate its ultimate value in the treatment of this disease.

The prognosis in optic neuritis varies with the cause. If the condition is due to multiple sclerosis, the immediate prognosis is good and recovery usually occurs. Repeated attacks may leave permanent sequelae. However, complete blindness rarely occurs. Multiple sclerosis rarely attacks both optic nerves at the same time. Conditions which attack both optic nerves simultaneously in general do not have as good prognosis as those involving only one nerve.

FUNDUS FINDINGS IN BLOOD DISEASES

The outstanding changes in diseases of the blood are retinal hemorrhages of various types. The hemorrhages tend to be linear or of the large flat type. White centered hemorrhages are common especially in leukemia and pernicious anemia. White centered hemorrhages are not diagnostic of any particular condition but are suggestive of both these diseases. Cotton-wool patches may be observed. If severe anemia is present, the disk is pale. In leukemia, the number of hemorrhages seems to be related to the degree of anemia.[2] The veins show tremendous dilatation and assume a sausage-like appearance. Along with this venous change, an alteration in the color of the fundus occurs; the entire fundus takes on an orange hue. When present, these fundus changes are practically diagnostic of leukemia. However, all cases of leukemia do not show fundus changes. In a total of 138 cases, Borgenson and Wagener[3] found retinal changes in 70 per cent of the acute cases and in 63 per cent of the chronic cases.

In polycythemia, fundus changes are usually not observed unless the cell count reaches 8,000,000 and the hemoglobin 115 per cent.[4] When present, they consist of dilatation and tortuosity of both the arteries and veins but the veins are especially affected. In contrast to the color change observed in leukemia, the fundus in polycythemia takes on a purplish red hue. Hemorrhages and exudates are uncommon, but blurring of the disk margins is often observed. True papilledema may be observed. Vision usually remains good in spite of the papilledema.

In subacute bacterial endocarditis and in other conditions which are prone to give rise to infective emboli in the blood stream, fundus changes may be observed. The changes encountered depend upon the virulence of the bacteria in the emboli and upon the size of the emboli. If the emboli are small and the bacteria of low virulence for the retina, as is the case in subacute bacterial endocarditis, small abscesses appearing

similar to white centered hemorrhages may be seen in the vicinity of the disk. This fundus picture has been designated as Roth's septic retinitis, and is practically diagnostic of subacute bacterial endocarditis. It is observed in only a few of the patients with this condition, however. If the emboli are of high virulence for the retina, as in some cases of septicemia, the entire retina and indeed the globe itself may be consumed with an overwhelming purulent infection — a metastatic panophthalmitis. If the emboli are large, an occlusion of the central retinal artery may result.

FUNDUS FINDINGS IN SYSTEMIC HYPERTENSION AND DIABETES MELLITUS

Hypertension. The changes which may occur in the retina in hypertension are as follows: generalized narrowing of the retinal arterioles with or without generalized sclerosis, focal narrowing of the arterioles with or without focal sclerosis, arteriolar or venous occlusion, sheathing of retinal vessels, cotton-wool patches, snowbank exudate around the disk, hard exudates, retinal and vitreous hemorrhages, retinitis proliferans, flat detachment of the retina, and papilledema. The first changes invariably occur in the arterioles. These consist of generalized or focal narrowing or both. As time passes, sclerosis of the retinal arterioles occurs. Sclerosis thus indicates a hypertension of some duration — usually years. Sclerosis is recognized by the widening and brightening of the light reflex running down the center of the arteriole and also by the changes evident at the arteriole–vein crossings. These crossing changes consist in decreased transparency of the overlying arteriole where it crosses the vein, making it difficult or impossible to see the underlying venous column. The vein also takes on a "nicked" appearance, which is the result of compression of its blood column by a sclerotic arteriolar wall. The angle of crossing of arterioles and veins changes from a normal acute angle to one approaching a right angle. This last change is one of severe sclerosis, however. In judging sclerosis of retinal arterioles, it must be borne in mind that brunets and all those with fairly heavy skin pigmentation normally show a more prominent light reflex on the arteriolar blood column than do those of fair complexion.

Hemorrhages and exudates may be present without sclerosis of the retinal arterioles but not without either general or focal narrowing of the arterioles. The hemorrhages and exudates (cotton-wool patches or hard exudates) are similar to the lesions found in the fundus in other conditions. Thus, the key to the diagnosis of the cause of retinopathy present in a given patient rests with the study of the retinal arterioles. If the retinopathy is due to hypertension, diagnostic findings are present in the retinal arterioles. Hypertension in the retina is strictly an arteriolar disease and all changes in the retina are related to these arteriolar alterations. Whether the arteriolar changes are secondary to the elevated blood pressure and represent an attempt to maintain normal retinal hemodynamics or whether they are a primary change participating in the cause of the hypertension must remain unanswered for the present.

Cotton-wool patches are acute lesions and indicate a sudden rise in blood pressure. They are of serious import and are an indication for immediate treatment of the hypertension. They may be found in a hypertension of longstanding, in which case they are superimposed upon other chronic fundus changes and point to a recent exacerbation of the blood pressure. Many cotton-wool patches are the result of occlusions of small arterioles and thus are retinal infarcts.

Hard exudates indicate chronicity[5] and represent small collections of phagocytic cells which have engulfed debris from the injured retina.

In essential hypertension, the degree of sclerosis of the retinal arterioles correlates quite well with the degree of sclerosis of the kidney arterioles,[6] and thus the eye findings may be used as a guide to the severity of the kidney damage.

The presence of papilledema is of grave prognosis; patients live on the average of thirteen months after onset of papilledema. Numerous exceptions to this average are found, however.

Any treatment which lowers the blood pressure gradually improves the fundus picture. However, there is some danger in precipitating occlusion of retinal vessels by excessive and rapid lowering of blood pressure in a patient with pronounced arteriolosclerosis of retinal vessels.

We usually think of essential hypertension when we are discussing retinal changes in hypertension, but it must be understood that any disease which gives rise to hypertension will produce the picture we have been considering. The etiologic diagnosis of the hypertension cannot be made from the fundus picture alone, although because of the varying character of the hypertension in different disease states shrewd guesses can sometimes be made. Other diseases which may produce hypertensive changes in the fundus are glomerulonephritis, toxemia of pregnancy, pheochromocytoma of the adrenal, Cushing's basophilic adenoma of the pituitary, disseminated lupus erythematosus, and periarteritis nodosa.

Diabetes mellitus. The changes which may occur in the retina in diabetes mellitus are as follows: capillary aneurysms, hard exudates, tortuosity and irregularity in caliber of the retinal veins, proliferation of new vessels especially from the venous side of the circulation, retinal hemorrhages, vitreous hemorrhages, retinal detachment, and arteriolosclerosis.

The sequence of changes is roughly as follows:

Grade I—retinal capillary aneurysms with or without small retinal hemorrhages.

Grade II—the changes of grade I plus hard exudates.

Grade III—the changes of grade II plus visible changes in the retinal veins consisting either of irregularity in caliber of the veins or proliferation of new venules on the surface of the retina. Often retinal hemorrhages and retinal arteriolosclerosis occur.

Grade IV—the changes of grade III plus hemorrhages into the vitreous and proliferation of vessels with connective tissue into the vitreous. At times retinal detachment is present.

It is proper to set up a grading of the lesions such as just given for purposes of classification, but we must remember that nature draws no such sharp dividing lines. The changes of diabetes are no exception. At times we find dilatation and tortuosity of the larger retinal veins as one of the earliest signs of diabetes. These changes may occur simultaneously with the onset of the microaneurysms.

It is important to realize that although the diabetic is more prone to develop retinal arteriolosclerosis than the normal individual and with it hypertension, diabetes is primarily a disease of the veins and capillaries. Retinopathy occurs in the diabetic in the presence of normal retinal arterioles and is in no way dependent upon arteriolar changes for its inception. Retinopathy in hypertension never occurs in the presence of normal retinal arterioles. After the diabetic develops hypertension, he will of course have superimposed hypertensive alterations upon his underlying diabetic changes. He is then said to have a mixed retinopathy and the underlying diabetic changes may be more difficult to diagnose. Focal and general narrowing of the retinal arterioles signal the presence of hypertension in the diabetic. Cotton-wool patches may also be present in the hypertensive diabetic.

Microaneurysms in the diabetic are recognized as small, red, smooth-edged dots in the fundus. These dots persist for months but may disappear without leaving a trace. The hard exudates of diabetes have a more yellowish tint than those of hypertension, but the difference in color is not consistent enough to be diagnostic. At this point the so-called colloid bodies and the retinopathy of the aged should be mentioned. Both of these conditions may be confused with the retinopathy of diabetes. Colloid bodies are found in normal eyes of any age group and consist of round, yellowish deposits in the retina. They may be mistaken for the exudates of diabetes and hypertension. They are actually excrescences of Bruch's membrane and are distinguished by their round smooth edge and very faint ring of pigment. This slight increase of pigment density around their border is a subtle but important differential point. They vary in diameter from one-half the size of a retinal vessel at the disk to several times the diameter of a vessel, assuming a plaque-like appearance in the larger sizes. They are of no significance from the standpoint of general health.

Some aged people may show hemorrhages and exudates resembling diabetic retinopathy and yet do not have diabetes. This retinopathy is often most prominent in the macular region and we must attribute it to local, senile, vascular degenerative changes. The small aneurysms and the proliferation of new venules are usually lacking in this senile condition, however.

Diabetic retinopathy is a part of the Kimmelstiel-Wilson syndrome which is characterized by edema, hypertension, albuminuria, and retinopathy. The diagnosis of the characteristic kidney lesion of the syndrome cannot be made from the presence of any particular fundus finding, but the more severe the retinopathy the greater the possibility that the patient has the characteristic kidney lesion. The severity of the retinopathy seems to correlate quite well with the degree of reduction in kidney function.[7] The hyaline nodules in the kidney likewise do not occur in the absence of retinopathy.[8] The fact must be remembered, however, that the onset of retinopathy in diabetics is not of the same serious import with regard to the life of the patient as is the onset of retinopathy in hypertension.

The cause of diabetic changes in the fundus is unknown. Opinion differs as to whether control of the diabetes influences the onset of retinopathy. All are agreed that the severity of the retinopathy is directly proportional to the duration of the diabetes. Until more is known with regard to other factors in diabetes, it would seem advisable to "control" the diabetic as accurately as possible. Control from the standpoint of the ophthalmologist consists of avoiding excessive hyperglycemia and wide fluctuations in the blood sugar. These regulations should be accompanied by a fairly high protein diet and some

restriction of fats. A careful study by Sherrill[8] showed that control of the diabetes minimizes danger of the development of severe retinopathy.

The diabetic with retinopathy usually has increased capillary fragility but rutin has proved rather disappointing in the treatment of the retinopathy.[9]

With increased longevity of the diabetic made possible by insulin, the eye damage has become the primary complication of diabetes. The incidence of retinopathy in diabetics has shown a threefold increase from 1925 to 1950. It is hoped this problem will be solved in the near future.

MISCELLANEOUS FUNDUS CONDITIONS

Obviously all fundus manifestations of systemic disease are impossible to cover in a single paper. The few conditions which I am now going to briefly discuss do not complete the list by any means but, if mentioned, will perhaps permit this article to be worthy of its title.

Choroiditis (chorioretinitis). In this condition, the eye manifestations are usually the most important indication of the disease. Unfortunately in many instances no systemic cause can be found. Some of the known causes of the condition are brucellosis, syphilis, tuberculosis, toxoplasmosis, sympathetic ophthalmia, and virus infections. Treatment in general is unsatisfactory unless the cause can be found and eradicated.

Disseminated lupus erythematosus. As we have already seen, this condition may present the fundus findings of hypertension. However, at times characteristic fundus changes are present in the absence of any hypertension. These fundus changes consist of small cotton-wool-like patches in the retina in the presence of normal or nearly normal retinal arterioles. On pathologic examination, these cotton-wool-like patches apparently are cytoid bodies. The nature and origin of cytoid bodies are unknown, but it does seem reasonable to postulate that in this disease they may be the result of occlusion of small arterioles. In any case they may be of considerable help in the diagnosis and are of serious prognosis. Similar lesions have been reported in dermatomyositis, periarteritis nodosa, and serum sickness. Periarteritis nodosa rarely involves the retinal vessels directly, at least as far as visible lesions are concerned. The choroidal vessels may show nodules, however.

Buerger's disease. In this disease, the retinal vessels may rarely show a perivasculitis and occlusion resulting in blindness of the affected eye.

Raynaud's disease. In Raynaud's disease, spasm and occlusion of the central retinal artery may occur.

The phakomatoses. This group of diseases includes von Recklinghausen's disease, tuberous sclerosis, Sturge-Weber syndrome, Lindau-von Hippel disease. Each disease presents certain eye manifestations. Space does not permit a discussion of these manifestations.

Tay-Sachs disease. In this disease of infants, the retinal ganglion cells show degeneration with accumulation of lipoid substances within the cell bodies. Because of the great concentration of ganglion cells around the fovea, the macular region appears whitish with a central red spot. The appearance is that of an ice cream cone with a red cherry in the center and is diagnostic of the disease. Death occurs by the time the child is 3 years of age. A similar fundus picture may be observed in Niemann-Picks disease.

Vogt-Spielmeyer or Batten-Mayou type of amaurotic family idiocy. This condition is somewhat related to Tay-Sachs disease but comes on a little later in life, from the fifth to eighth year, and has a different fundus picture. The fundus in this disease shows pigmentary changes in the macular region resembling those of senile macular degeneration. In addition, however, usually peripheral pigment changes resembling retinitis pigmentosa are present; the retinal vessels are narrowed; and the optic disk is pale. The visual loss may precede visible fundus changes. Fundus changes usually precede mental deterioration.

SUMMARY

This paper has discussed the most common fundus manifestations of general disease and briefly mentioned some of the more rare conditions. Emphasis has been placed upon the importance of the eye findings in the diagnosis and prognosis of systemic disease. The differential diagnosis of various fundus lesions has been delineated.

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The Role of the Pituitary-Adrenal System in Rheumatic Fever

VINCENT C. KELLEY, M.D.
Salt Lake City, Utah

THE BODY of evidence implicating group A beta-hemolytic streptococcus as the initiating agent of both first attacks and recurrences of rheumatic fever has become so imposing as to eliminate any reasonable doubt that, at least in most instances, this organism is responsible for the initiation of the attack. This evidence has arisen from (1) clinical epidemiologic studies[1-17] showing a high incidence of streptococcic infections preceding rheumatic attacks, a similar pattern of seasonal variation in incidence of streptococcic infections and of rheumatic fever, and the occurrence of "epidemics" of rheumatic fever in crowded areas; (2) studies of specific antibodies to streptococcus and streptococcic products in patients with rheumatic fever, including antistreptolysin O, antistreptokinase, antihyaluronidase, streptococcic agglutinins, type-specific anti-M precipitins, and bacteriostatic antibodies and antibodies against group-specific C carbohydrates and streptococcic nucleoproteins;[10, 18-36] and (3) studies of prevention of rheumatic fever by the prophylactic use of sulfonamides or penicillin[17, 37-56] and by early treatment of streptococcic infections.[17, 57-64]

However, despite this mass of evidence implicating streptococcus in the initiation of most attacks of rheumatic fever, several reports have implicated other precipitating factors, including other infections, fractures, burns, skin rashes, penicillin, tetanus toxoid, smallpox vaccination, traumatic injury, malaria, and dysentery.[8, 65-69] In none of these studies was the possibility eliminated that concomitant streptococcic infections existed. However, even if these reports were accepted at face value, it would not alter the inevitable conclusion that most cases of rheumatic fever are initiated by a preceding streptococcic infection.

ROLE OF THE HOST IN RHEUMATIC FEVER

Whether or not streptoccocic infection invariably precedes the onset of rheumatic fever, rheumatic fever does not invariably follow all streptococcic infections. Rather, only a small percent of previously well individuals who contract a streptococcic infection develop rheumatic fever as a sequela. This proportion is surprisingly constant and has been reported to approximate 3 per cent by several investigators who have dealt with patients infected with different serologic types of group A beta-hemolytic streptococcus and with different clinical forms of streptococcic infection.[69-71] However, when streptococcus epidemics occur in rheumatic populations, the incidence of reactivation of rheumatic fever in these subjects is comparatively very high.[72-79] The occurrence of these relatively constant ratios between number of streptococcic infections and number of rheumatic sequelae and the greater incidence of rheumatic sequelae following streptococcic infections in groups known to be susceptible to rheumatic fever than in the general population, in addition to considerable other evidence, have led to the concept of host variability with regard to susceptibility to rheumatic fever.

The factors which determine the reaction of the host to a streptococcic infection, especially those which determine whether or not rheumatic sequelae will develop after that infection, are not understood even though many attempts have been made to delineate them. It has been postulated that rheumatic susceptibility is an hereditary trait transmitted by a mendelian recessive gene.[80-85] However, the evidence presented in these studies has not been considered conclusive. A more recent study[86] presents data which seem to indicate rather convincingly that rheumatic susceptibility is an hereditary trait, although the exact mendelian pattern of inheritance is not clear. If it be granted that rheumatic susceptibility is inherited, the problem still remains of defining the special physiologic and anatomic attributes which are inherited that make the patient susceptible to rheumatic fever. Many attempts have been made to determine what the characteristics might be, but these efforts have met with little success.

One approach to clarification of what the

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

characteristics determining rheumatic susceptibility may be is through the identification of biochemical or physiologic differences existing between patients with rheumatic fever and the remainder of the population. During the past few years, a rather extensive literature has grown up concerning biochemical abnormalities which occur during the acute phase of rheumatic fever.[87] Those substances whose concentrations are characteristically and nonspecifically altered during the course of acute disease have been designated as "acute-phase reactants" or "acute-phase substances." Among the acute-phase reactants and reactions may be included the nonspecific hyaluronidase inhibitor,[88-96] C-reactive protein,[97-101] serum mucoproteins,[94, 95, 102-105] serum nonglucosamine polysaccharides,[106-114] serum hexosamines,[115-119] serum complement, [120] bactericidins,[121-123] diphenylamine reaction,[124,125] and the quaternary ammonium salt reaction.[126, 127] This list could be extended considerably if all substances and reactions which have been suggested as belonging to this group were included. In addition to these many nonspecific changes which occur in the blood, there are characteristic changes in the distribution of the electrophoretic protein fractions[128] and the first appearance or appearance in increased titer of the various specific antistreptococcic antibodies[35] reflecting the preceding streptococcic infection. However, none of these changes which occur during the acute phase of rheumatic fever is specific for this disease and none persists beyond the period of rheumatic activity. It would seem that these changes could have little to do with rheumatic susceptibility.

IS ADRENAL INSUFFICIENCY A FACTOR?

Evidence previously has been presented[95, 96, 105, 129-131] that serum levels of certain acute phase reactants are controlled or greatly influenced by the adrenal cortex. Since the levels of these acute-phase reactants are increased in the blood of patients with acute rheumatic fever and approach normal again as the disease becomes quiescent, it seems possible that altered adrenocortical function exists in patients with this disease. Especially interesting in this connection is the nonspecific hyaluronidase inhibitor. This acute-phase reactant first was shown by Good and Glick[93] to be elevated in the blood of patients during the acute phase of rheumatic fever and to be present in lower than normal concentrations in patients with "convalescent" rheumatic fever, inactive rheumatic fever, or Sydenham's chorea. Soon thereafter, it was reported[95, 96] that, during hormone therapy of rheumatic fever, the hyaluronidase-inhibitor level rapidly decreased from an initial high value and thereafter remained at normal or decreased concentrations in the blood. Although this inhibitor even yet has not been identified structurally and can be measured only in terms of its ability to inhibit hyaluronidase, it has been shown to be related directly to the functional state of the adrenal cortex in that (1) it is present in high concentration in the blood of acutely ill patients or in those who have been exposed to rather severe stress, (2) it is present in lower than normal concentration in adrenalectomized or hypophysectomized animals, and (3) its concentration in the blood is increased following the administration of ACTH and especially after the administration of cortisone. The observation that the level of this inhibitor is low in patients with rheumatic fever except during the early acute phase was therefore suggestive of abnormal adrenocortical function in such patients.

A completely different line of reasoning also had led to the conclusion that adrenocortical function probably was abnormal in patients with rheumatic fever. The original demonstration by Hench and associates,[132] as well as the numerous reports which rapidly followed from various laboratories,[133-141] of the beneficial effects of both cortisone and ACTH on the acute manifestations of rheumatic fever were interpreted by many as suggesting the presence of a state of adrenocortical insufficiency in patients with this disease. However, other interpretations explaining the effects of these hormones in rheumatic disease also have been advanced. Among these, as listed by Sayers,[142] are: (1) interference with the release of the toxic action of the anaphylactogenic substance of the antigen-antibody reaction,[143] (2) alterations in cell permeabilities to the action of hyaluronidase, [144, 145] and (3) suppression of mesenchymal tissue.[146] In addition, it has been proposed[147] that, in collagen diseases, certain tissue (for example, connective tissue) may be relatively insensitive to adrenocortical hormones. If this concept is correct, the defect in patients with rheumatic fever is not in the pituitary-adrenocortical system but is in the response of peripheral tissues.

Several attempts have been made to determine whether or not there is pituitary-adrenocortical insufficiency in patients with rheumatic disease.[148-155] In all of these, indirect response tests have been employed, and no consistent impairment of adrenocortical function in patients with rheumatic disease has been detected.[148] After

reviewing the literature concerning the possible mechanism of action of hormones in therapy of rheumatic states, Sayers[142] concluded that the effects of the hormones are entirely pharmacologic rather than physiologic, since " . . . if the effect were physiological, then the hormones would be expected to replace a deficiency. However, patients with collagen disease do not have a metabolic derangement characteristic of adrenal cortical insufficiency."

DIRECT DETERMINATION OF CONCENTRATIONS OF PITUITARY-ADRENAL HORMONES

Only recently has it become possible to study directly the concentrations of pituitary and adrenal hormones in the blood. In a preceding paper, Ely has outlined the development and present status of technics for clinical studies of these hormones.[156] Application of these methods to the study of rheumatic fever patients has permitted a more satisfactory evaluation of the status of pituitary-adrenal function in individuals with this disease than was possible previously.

It has been demonstrated that compound F, hydrocortisone, is the principal adrenocortical hormone in man.[157] This compound is one of a group of adrenal steroids, the 17-hydroxycorticosteroids, which also includes compounds E (cortisone) and S. The technic of Nelson and Samuels for plasma 17-hydroxycorticosteroids[158] permits a direct chemical determination of the concentration of these steroids in plasma. Since compound F is present in much greater quantities than are the other 17-hydroxycorticosteroids, this determination may be considered as reasonably specific for this compound.

Table 1 presents data concerning 17-hydroxycorticosteroid concentrations in children with active and inactive rheumatic fever.

TABLE 1
PLASMA 17-HYDROXYCORTICOSTEROIDS IN CHILDREN WITH RHEUMATIC FEVER

	Plasma 17-hydroxycorticosteroids (μg. per cent)				
Group	*No.*	*Mean*	*S.E.M.*	*Range*	*p (vs. controls)*
Controls	40	12	±1.29	0-28.7	
Well-established, active rheumatic fever	31	5.9	±0.93	0-16.1	<0.01
Inactive rheumatic fever	87	8.3	±0.61	0-19.8	<0.01

Those patients designated in the table as having well-established, active rheumatic fever had been ill for more than two weeks. In this group, the mean concentration of plasma 17-hydroxycorticosteroids was 5.9 ± 0.93 μg. per cent, a figure significantly lower than the mean value observed in the control group. Patients with inactive rheumatic fever had a mean plasma 17-hydroxycorticosteroid concentration of 8.3 ± 0.61 μg. per cent. This value also is significantly lower than that which was observed in the control group.

Whereas not much importance can be attributed to a single low 17-hydroxycorticosteroid value, consistently low values in the same individual or in a group of individuals in the same clinical classification are significant. The low plasma 17-hydroxycorticosteroid concentrations observed in rheumatic fever patients do not mean necessarily that the adrenal cortex in these patients does not or cannot produce its hormones so rapidly or in so great a quantity as in the normal individual. An attractive alternative explanation is that, in such individuals, adrenal steroids are destroyed or removed from the blood more rapidly than they are replaced by the adrenal cortex. Also, it seems possible that some adrenal hormone other than 17-hydroxycorticosterone, compound F, may be present in the blood of these individuals in sufficient concentration to usurp the role of the latter in regulating the pituitary release of ACTH. Thus, the equilibrium state with regard to release of pituitary ACTH might be such as to provide insufficient stimulation to the adrenal cortex to maintain circulating concentrations of 17-hydroxycorticosteroids as high as they are in "normal" individuals.

Even if one of these latter explanations were correct, it would not alter the fact that the equilibrium state with regard to 17-hydroxycorticosteroids in individuals with rheumatic fever indicates that the adrenal cortex is not producing these steroids rapidly enough to maintain a normal concentration in the blood. Therefore, homeostatic mechanisms which are adequate to maintain certain levels of circulating 17-hydroxycorticosteroids in normal individuals are not adequate to maintain similar levels in patients with rheumatic fever.

Data presented so far do not eliminate the possibility that the anterior pituitary rather than the adrenal cortex is to be implicated in the failure of patients with rheumatic fever to maintain usual circulating concentrations of 17-hydroxycorticosteroids. In an attempt to evaluate this possibility, the circulating concentrations of endogenous ACTH in the blood of patients with rheumatic fever were determined. The results of these studies are shown in table 2. The technic used was that of Sydnor and Sayers,[159] which employs oxycellulose extraction of the ACTH from blood using a modification of the Ast-

wood[160] procedure followed by determination of the ACTH concentration of the extract by the adrenal ascorbic acid-depletion method of Sayers and associates.[161]

TABLE 2
BLOOD ACTH CONCENTRATIONS IN PATIENTS WITH RHEUMATIC FEVER

Group	Number of subjects	Number of determinations	Blood ACTH in mμ/Liter		Number of samples with detectable ACTH
			Mean	Range	
Normal children	9	9	0	0	0
Well-established, active rheumatic fever	16	17	14.4	0-87.8	15
Inactive rheumatic fever	9	17	6.5	0-17.4	15

In the patients with active rheumatic fever who had been ill two to twenty-five weeks, 15 of 17 determinations revealed measurable ACTH levels with no evidence of a trend towards either increasing or decreasing values with increasing duration of illness. In patients with inactive rheumatic fever, 17 determinations of blood ACTH on 9 different patients who had exhibited no evidence of rheumatic activity or had any form of therapy for at least ten weeks and up to two years are included in this table. In 15 of the 17 samples, there were elevated concentrations of ACTH. In each of 2 patients, 1 sample had no detectable ACTH; in each of these patients, as in several others of this group, duplicate samples for assay had been obtained within a week. Each patient whose ACTH level was zero on 1 determination had a definitely elevated concentration of ACTH in a duplicate sample, although in neither case was any detectable change in the patient's clinical status noted during the interim between obtaining blood samples.

Thus, patients with well-established, active rheumatic fever or inactive rheumatic fever have elevated concentrations of ACTH and abnormally low concentrations of 17-hydroxycorticosteroids in their blood. In these patients, the adrenal cortex, stimulated by much greater than usual concentrations of ACTH, does not respond by production of 17-hydroxycorticosteroids in quantities sufficient to maintain the circulating concentrations of these steroids as high as normal. Regardless of whether this represents inadequate production of steroids as compared to that of normal individuals or inability of the cortex to produce the steroids in sufficient quantity to compensate for an increased rate of utilization by tissue, at equilibrium, the adrenal cortex is not producing steroids fast enough to maintain normal plasma levels. The hormone pattern here is similar to that observed in patients with Addison's disease[157,162,163] and in adrenalectomized animals[164] and is interpreted as indicating adrenal insufficiency in patients with rheumatic fever.

The observations of high ACTH concentrations and low 17-hydroxycorticosteroid concentrations in patients with *inactive* rheumatic fever may be of special significance. It is not clear from data at hand whether adrenal insufficiency is a result of rheumatic fever or whether it exists in these individuals previous to the first attacks of rheumatic fever and might be a factor in the pathogenesis of this disease. However, it seems apparent that, once a patient has had an attack of rheumatic fever, his pituitary-adrenal hormone pattern remains abnormal. It is well known that patients with inactive rheumatic fever who develop streptococcic infections are much more prone to recurrent attacks of rheumatic fever than are individuals who have not had this disease.[72-79] No satisfactory explanation has been advanced for this difference in response.

Any measurable chemical or physiologic abnormality occurring regularly in patients with inactive rheumatic fever, a group known to be rheumatic-susceptible, may well occur with similar regularity in other rheumatic-susceptible individuals. Conceivably, the adrenal insufficiency which occurs in patients with rheumatic fever may have existed before first attacks of this disease and might be the factor that caused them to be included in the 3 per cent[69-71] of the normal population who develop rheumatic fever as sequela to untreated streptococcic infection. If this were true, all rheumatic fever patients would have adrenal insufficiency—a situation suggested as existing by the data presented here—and would have an increased liability to develop rheumatic fever attacks following steptococcic infection—an established fact.

Recent genetic studies[86] indicate that inheritance of rheumatic fever susceptibility is probably a reality. If, as seems likely from analogy with published data concerning the nonspecific hyaluronidase inhibitor,[93,165] the adrenal insufficiency antedates the occurrence of rheumatic fever in an individual, it appears at least possible that the hereditary trait which determines rheumatic fever susceptibility might be this adrenal insufficiency. The demonstrated efficacy of prophylaxis in preventing rheumatic recurrences implies that a similar efficacy in preventing the

initial attacks of rheumatic fever is possible were there a means of consistently detecting the susceptible individuals. Thus, the reported observations of low 17-hydroxycorticosteroid levels and high ACTH levels in patients with inactive rheumatic fever are of considerable potential importance and deserve extensive investigation.

"SEGMENTAL" ADRENAL INSUFFICIENCY

Segmental adrenal insufficiency is now a well-established entity. For example, in congenital adrenal hyperplasia there is a specific impairment in the ability to produce 17-hydroxycorticosteroids which exists concurrently with overproduction of adrenal androgens.[166, 167]

Since there are no data concerning the concentrations of adrenal steroids other than the 17-hydroxycorticosteroids in patients with rheumatic fever, adrenal insufficiency in these patients also may be segmental in nature, involving only this particular group of steroid hormones. This concept would explain the absence of any symptoms ordinarily attributed to adrenal insufficiency in patients with rheumatic fever. According to Cheng and Sayers,[168] desoxycorticosterone treatment leads to a state of hormone imbalance characterized by an excess of DCA and a deficiency of endogenous 11-17-oxysteroid production. "The role of the deficiency state as well as that of the excess DCA must be considered in arriving at conclusions regarding the etiological role of DCA in the production of pathological conditions of the cardio-vascular system." The pathology produced by DCA in experimental animals may be due to a lowering of resistance of the tissues as well as a result of a deficiency of 11-17-oxysteroids. In conformity with this postulation are experiments of Woodbury and associates,[169] indicating that simultaneous administration of ACTH and DCA inhibits development of pathologic changes induced by DCA alone.

The aforementioned need not necessarily imply that DCA is the hormone which is secreted in excessive amounts by the adrenal cortex in the patient with rheumatic fever, although this is a possibility which must be considered. At the present time, we are investigating this possibility by 2 approaches. Desoxycorticosterone has been reported[170] to be formed by the adrenal cortex through a series of slow chemical reactions converting cholesterol to desoxycorticosterone. Once formed, the desoxycorticosterone is converted rapidly to corticosterone. If desoxycorticosterone is being produced by the adrenal cortex in excessive amounts, one might be able to detect increased amounts of corticosterone in the blood of patients with rheumatic fever. At the present time, a study of corticosterone concentrations in rheumatic fever patients is under way in our laboratory. In addition, measurement of total corticosteroids by the method of Nelson and Calver[171] in patients with rheumatic fever should indicate whether or not some steroid other than the 17-hydroxycorticosteroids is being produced in excessive amounts. If the total corticosteroid concentrations are high in patients with rheumatic fever while at the same time the 17-hydroxycorticosteroid concentrations are low, it would indicate that these patients have a segmental adrenal insufficiency. Results in a few preliminary experiments suggest this may be true.

RELATIVE RATHER THAN ABSOLUTE ADRENAL INSUFFICIENCY

As mentioned earlier, numerous studies of adrenocortical function employing eosinophil response tests as criteria have failed to elicit evidence of impairment of adrenocortical function in rheumatic fever patients. In our laboratory, adrenal responsiveness in patients with rheumatic fever has been studied in 3 ways. (1) The epinephrine-eosinophil response test revealed that the response of the eosinophils was no different in patients with rheumatic fever than in normal individuals. However, it should be recalled in this regard that this test is no longer considered a valid criterion of adrenal function,[172-175] since it does not reflect any known function of the adrenal cortex and since it may be normal in adrenalectomized animals and patients. (2) The ACTH-eosinophil response test, a more reliable criterion of adrenocortical function, likewise revealed no differences between rheumatic and normal individuals. It has been shown that, following ACTH stimulation, the response of eosinophils does not correlate well with the response of 17-hydroxycorticosteroids,[176] the principal adrenocortical hormones. (3) When a standard ACTH-17-hydroxycorticosteroid response test was employed, there again was observed no difference in response between the patients with rheumatic fever and normal children.[177, 178] This test, as performed, employed a dose of 25 I. U. ACTH, as did the ACTH-eosinophil response test. This dose, of course, is excessively large when compared to even the highest concentration of endogenous ACTH yet observed in any patient with rheumatic fever, representing many times the estimated total amount of circulating endogenous ACTH in these patients. This response of patients with rheumatic fever to the administration of a rela-

tively large test dose of exogenous ACTH distinguishes them from patients with Addison's disease or congenital adrenal hyperplasia and from adrenalectomized animals or patients, since none of the latter are able to respond by elevation of 17-hydroxycorticosteroid concentrations regardless of the dose of ACTH administered. This finding indicates that adrenal insufficiency in patients with rheumatic fever is *relative* rather than absolute, since at some level of stimulation the adrenal is able to respond adequately.

Not only do these patients respond adequately to large test doses of exogenous ACTH, but, as shown in table 3, they also respond with elevations in circulating steroid concentrations during the early acute phase of a rheumatic attack.

TABLE 3

PLASMA 17-HYDROXYCORTICOSTEROIDS IN PATIENTS DURING EARLY STAGES OF RHEUMATIC FEVER ACTIVITY

	Plasma 17-hydroxycorticosteroids (μg. per cent)				
Group	*Number of Patients*	*Mean*	*S.E.M.*	*Range*	*p (vs. controls)*
Controls	40	12.	±1.29	0-28.7	
Early acute rheumatic fever	15	23.1	±1.49	14.1-35.2	<0.01
Transitional phase	12	11.8	±2.01	0-30.2	>0.5

Those patients designated in the table as having early acute rheumatic fever had been ill not more than one week. In this group, the mean plasma 17-hydroxycorticosteroid concentration was 23.1 ± 1.49 μg. per cent. Thus, these patients had significant elevations of the plasma 17-hydroxycorticosteroid concentrations. This is in conformity with observations reported elsewhere[157,179] of elevated plasma concentrations of these steroids during the acute phase of many illnesses.

During the second week of active rheumatic fever, the 17-hydroxycorticosteroid values were extremely variable. In table 3, the patients of this group are designated as having a transitional phase of rheumatic activity. In this group, the mean steroid concentration was 11.8 ± 2.01 μg. per cent, a value which does not differ statistically from that in the control group. The wide variations observed in the transitional-phase group, 0-30.2 μg. per cent, probably are attributable to: (1) the rapid decrease in circulating concentrations of 17-hydroxycorticosteroids which occurs after the first few days of illness, (2) inaccuracies in determining precisely the date of initial symptomatology in many patients, (3) variations in the severity of the disease, and (4) individual variations in the endocrine response to the stress occasioned by the illness.

The occurrence of elevated 17-hydroxycorticosteroid concentrations during the early acute phase of rheumatic fever suggests that a heightened stimulus for adrenocortical secretory activity may exist at this time. It also suggests that the adrenal cortex of the rheumatic fever patient is capable of responding to this stimulus, at least early in the course of the illness. Elevated plasma steroid concentrations occur not only in patients suffering initial attacks of rheumatic fever, but also in those suffering acute recurrences of the disease. Since the latter group consists of individuals who had inactive rheumatic fever before the onset of acute recurrences, it seems likely that the adrenal cortex of the patient with inactive rheumatic fever, who is known to have relative adrenal insufficiency, is capable of responding to potent endogenous ACTH stimulation. The finding of elevated plasma steroid levels in patients with early acute rheumatic fever is interpreted as indicating a "stress response." An alternative explanation is an interference with factors concerned with removal of 17-hydroxycorticosteroids from the circulation. Preliminary data[180] obtained by determinations of the in vivo half-life of exogenous hydrocortisone in patients with rheumatic fever suggests that such may be the case.

Table 4 shows data concerning the concentrations of ACTH in the blood of patients during these same early stages of rheumatic activity.

During the early acute phase of rheumatic fever, at a time when the concentrations of circulating 17-hydroxycorticosteroids are consistently elevated, the circulating concentrations of endogenous ACTH are consistently low. This situation of simultaneously existing low ACTH concentration and high 17-hydroxycorticosteroid concentration seems somewhat paradoxical, since one might expect that a high concentration of ACTH in the blood would be needed to stimulate the adrenal to produce larger amounts of 17-hydroxycorticosteroids. However, previous reports[163,181] have indicated no detectable adre-

TABLE 4

BLOOD ACTH IN PATIENTS DURING EARLY STAGES OF RHEUMATIC FEVER ACTIVITY

	Blood ACTH (mU/liter)			
Group	*Number of patients*	*Mean*	*Range*	*Number elevated*
Controls	9	0	0	0
Early acute rheumatic fever	5	0	0	0
Transitional phase	6	14	0-25	5

nocorticotropic activity in the blood of patients with Cushing's disease. In addition, a patient with severe acute osteomyelitis[182] was found to have no elevation of blood ACTH despite markedly elevated circulating 17-hydroxycorticosteroids. Patients with Cushing's syndrome or severe acute disease such as osteomyelitis consistently have elevated concentrations of 17-hydroxycorticosteroids in the blood.[157, 158, 179] Thus, the situation of simultaneously occurring low ACTH concentration and high 17-hydroxycorticosteroid concentration reported here in patients with early acute rheumatic fever, although surprising, is not unprecedented. It is difficult to understand why ACTH concentrations are not elevated under these circumstances, but it may be that the high 17-hydroxycorticosteroid concentrations are "damping" pituitary release of additional ACTH. The half-life of ACTH, in vivo, is extremely short;[183] thus, in the absence of nearly continuous release by the pituitary, the ACTH concentration in the blood should be low. It is conceivable also that, if the rate of removal of 17-hydroxycorticosteroids from circulation is decelerated during the early acute phase as was suggested previously, there would result an accumulation of these steroids with consequent inhibition of pituitary release of ACTH.

By the second week of rheumatic activity, designated in the table as transitional phase, the ACTH concentrations are elevated almost uniformly as they are in patients with well-established, active rheumatic fever. Thus, it appears that only during the initial few days of illness is the response to endogenous ACTH stimulation adequate to maintain a pituitary-adrenal hormonal pattern similar to that seen in other acutely ill patients.

RELATIVE ADRENAL INSUFFICIENCY IN SYDENHAM'S CHOREA

Sydenham's chorea has been reported to occur as the primary manifestation in 20 to 30 per cent of rheumatic fever patients[184] and during some phase of the illness in 50 per cent.[185] It is considered to be so intimately related to rheumatic fever that it is included by Jones[186] as a major manifestation of the latter. Because of this intimate relationship, it seemed of interest to determine whether relative adrenal insufficiency, consistently found in patients with rheumatic fever, also exists in patients with chorea.

TABLE 5

PLASMA 17-HYDROXYCORTICOSTEROID CONCENTRATIONS IN PATIENTS WITH CHOREA

Group	Plasma 17-hydroxycorticosteroids (μg. per cent)				
	Number of patients	Mean	S.E.M.	Range	p (vs. controls)
Controls	40	12	±1.29	0-28.7	
Chorea	28	5.8	±0.84	0-12.8	<0.01

Table 5 shows the data concerning plasma 17-hydroxycorticosteroid concentrations observed in 28 patients with Sydenham's chorea. As shown in the table, the plasma 17-hydroxycorticosteroid concentrations were significantly lower in these patients than in the control group.

In table 6 are shown data concerning circulating ACTH concentrations in patients with chorea. In 7 patients with Sydenham's chorea, elevations of blood ACTH concentrations were not present as consistently as in other groups of rheumatic patients. Of 7 patients studied, 3 had elevated levels. An additional patient had an ACTH concentration calculated from the regression curve for the day which was higher than that of 1 of these 3 patients. However, the mean adrenal ascorbic-acid depletion for this assay fell within the range arbitrarily attributed to saline, and therefore the value is considered as zero for purposes of this report. Although the elevations in blood ACTH observed in these patients with chorea were not so great or so consistently found as in patients with exudative rheumatic fever, they definitely differ from the controls with regard to blood ACTH concentrations.

TABLE 6

BLOOD ACTH CONCENTRATIONS IN PATIENTS WITH SYDENHAM'S CHOREA

Group	Blood ACTH (mU/liter)			
	Number of patients	Mean	Range	Number of elevated values
Controls	9	0	0	0
Chorea	7	2.3	0-6	3

The existence of low 17-hydroxycorticosteroid concentrations and high ACTH concentrations in these patients suggests that in Sydenham's chorea, as in other phases of rheumatic fever, there exists adrenal insufficiency. That the adrenal insufficiency in these patients is *relative* rather than absolute is indicated by the data in table 7. The ACTH-17-hydroxycorticosteroid re-

TABLE 7

ACTH-17-HYDROXYCORTICOSTEROID RESPONSES IN PATIENTS WITH SYDENHAM'S CHOREA

Group	Plasma 17-hydroxycorticosteroids			
	Number of patients	Mean response* (μg. per cent)	S.E.M.	p (vs. controls)
Controls	40	17.8	±1.76	
Chorea	9	20.7	±5.13	>0.5

*Increase in plasma 17-hydroxycorticosteroid concentration two hours after 25 I.U. ACTH, intramuscularly.

sponses in the patients with chorea did not differ from those in the control group. Thus, in these patients also the adrenal insufficiency is *relative*. It seems worthy of comment that many of the chorea patients included in this study would be classified as "psychogenic chorea" by certain standards.[187]

RATIONALE FOR HORMONE THERAPY

The demonstration of a state of relative adrenal insufficiency in patients with rheumatic fever provides rationale for the use of hormone therapy in the treatment of this disease. Standard endocrinologic practice in therapy of hormonal deficiency states consists of replacement therapy with exogenous hormones. It would seem that in the same sense that if there is indication for cortisone in congenital adrenal hyperplasia, cortisone and DCA in Addison's disease, thyroid in cretinism, and insulin in diabetes, there is indication for cortisone in rheumatic fever. The fact that these patients have a *relative* rather than an absolute adrenal insufficiency, being capable of responding to ACTH stimulation by increasing their circulating concentrations of 17-hydroxycorticosteroids in a manner comparable with that in normal individuals, makes the use of ACTH therapy as logical as the use of cortisone. In conditions of absolute adrenal insufficiency, such as Addison's disease, the use of ACTH would be contraindicated despite the indication for the use of cortisone.

RATIONALE FOR SALICYLATE THERAPY

Similarities in the patterns of clinical response in patients treated with salicylates and in those receiving hormone therapy for rheumatic fever have been observed. In view of these similarities, considerable speculation has arisen concerning the possibility that the antirheumatic effects of salicylates are dependent upon stimulation of the pituitary-adrenal system. Cochran and associates[188] have reported the occurrence of Cushing's syndrome in a rheumatic patient receiving salicylate therapy. Eosinopenia[189-193] and adrenal ascorbic acid and cholesterol depletion[193-200] in response to salicylate have been reported and are apparently mediated through the pituitary.[193, 195, 197, 198] In addition, histologic indications of adrenal activation following salicylate administration have been observed.[194, 196]

Van Cauwenberge and Heusghem[201] found an increase in the urinary excretion of reducing steroids but not of neutral 17-ketosteroids in salicylate-treated patients. On the other hand, in guinea pigs given salicylates, Bertolani and associates[202] noted an increase in urinary excretion of 17-ketosteroids. Kelemen and colleagues[203] observed that salicylates did not alter the daily excretion of urinary "cortisone-active material" as determined biologically, and Smith and associates[204] found no increase in the urinary excretion of adrenocortical steroids as determined by paper chromatography. Salicylates have been reported to have an inhibitory effect on anaphylaxis,[205-207] serum vascular disease,[208-211] experimental inflammation,[212-214] and skin sensitivity reactions.[205, 215] ACTH and cortisone have been reported to have similar effects.[143, 216-227]

Inhibition of hyaluronidase by salicylates has been reported,[228-231] and an inhibitor of hyaluronidase has been found in the urine of salicylate-treated subjects.[232] Elevations in hyalurondise-inhibitor levels have been produced in normal individuals by the administration of ACTH or cortisone.[130, 233-236] Conversely, the abnormally high hyaluronidase-inhibitor levels occurring in acute rheumatic fever[91, 93, 237] decrease to normal in response to therapy with hormones.[95, 96, 238, 239] An increase in the urinary excretion of uric acid results from the administration of salicylates[189, 240] or of ACTH.[241-243] Both salicylates[244] and ACTH or cortisone[243, 245, 246] have been observed to cause a negative nitrogen balance. This mass of evidence that salicylates have many pharmacologic properties resembling those of ACTH and cortisone is most suggestive of a relationship between salicylates and the pituitary-adrenal system.

Studies in our laboratory, some of which were reported by Ely in a previous paper,[156] yielded certain results which would tend to strengthen the concept that the effects of salicylates in rheumatic fever are mediated by pituitary-adrenocortical stimulation. In these studies, it was found that in patients with salicylate intoxication and in guinea pigs given large doses of salicylates[247] there were consistent elevations of circulating 17-hydroxycorticosteroid concentrations. Such elevations were found to be mediated through the pituitary-adrenal system, since they did not occur in either adrenalectomized or hypophysectomized guinea pigs.[248] Later studies,[249] employing usual therapeutic doses of salicylates in normal human subjects, also gave evidence of an increased production of 17-hydroxycorticosteroids. However, there likewise arose from these studies some evidence that these steroids disappear from the circulation more rapidly under the influence of salicylates than in control subjects and that this rapid rate of disappearance is not accounted for by

urinary excretion of these steroids or of 17-ketosteroids. Because of the suggestive evidence that salicylates might produce their effect on rheumatic fever through influence on the pituitary-adrenal system, the studies to be reported here were performed in patients receiving salicylate therapy as well as those receiving hormone therapy for rheumatic fever. If salicylates do stimulate the pituitary-adrenal system in patients with rheumatic fever, there is rationale for their use in treatment of this condition similar to that advanced for the use of cortisone or ACTH.

INFLUENCE OF THERAPY ON THE ENDOCRINE PATTERN

Since it appeared there was rationale for hormone or salicylate therapy in patients with rheumatic fever, it seemed of interest to determine how therapy with these agents influenced the endocrine balance in patients with this disease. The results of these studies have been reported in detail elsewhere[178, 249] and will be mentioned here only briefly. During therapy with lyophilized ACTH administered intramuscularly or cortisone administered orally, circulating steroid levels were not elevated consistently throughout the therapy period. It has been demonstrated that the response in individuals receiving hormone therapy to a single dose of cortisone or ACTH is similar to that in normal individuals; a peak steroid elevation occurs approximately two hours after administration of the drug, and the steroid level returns to baseline value in four to six hours.

Therefore, in patients receiving repeated administrations of these hormones at approximately six-hour intervals, there probably occur a series of elevations and depressions of the circulating steroid concentration. On the other hand, while there may be fluctuations in the circulating steroid levels in patients treated with ACTH gel or with intramuscular cortisone, these levels consistently remain significantly elevated throughout the therapy period. It is interesting that no consistent differences have been observed as to the clinical effectiveness of therapy whether the former modes of hormone administration which cause only intermittent elevations of steroid concentrations or the latter ones which cause continuous elevations of steroid concentrations are employed. From these data it may be assumed that continuous elevations of circulating steroid concentrations are not requisite for a good therapeutic response.

Quite in contrast to the effects of hormone administration on circulating 17-hydroxycorticosteroid concentrations in rheumatic fever patients are those obtained following the administration of salicylates. In patients receiving salicylate therapy, the steroid concentrations do not become elevated; it appears from present data that these levels even may be depressed somewhat during salicylate therapy. Even in patients who develop clinical evidence of severe salicylate intoxication, there are no elevations of the circulating 17-hydroxycorticosteroid levels such as occur in previously normal individuals who develop salicylate intoxication.

Throughout hormone therapy with ACTH or cortisone in any form, there occur definite elevations in the urinary excretion of 17-hydroxycorticosteroids. On the other hand, during the period of therapy with salicylates, urinary steroid excretion is decreased as compared with that in the pre- or post-therapy period. Our present interpretation of these data is that, if the effect of salicylate on rheumatic fever is in any way mediated through the pituitary-adrenal system or its hormones, this probably occurs through increased utilization of the steroids rather than their increased production alone.

Data regarding the effects of cortisone therapy of rheumatic fever on circulating ACTH levels are presented in table 8. Although these data are inadequate to justify definite conclusions, it appears that the ACTH levels, which were elevated before initiation of cortisone therapy, become reduced to zero soon after its initiation. The first day after discontinuation of therapy, these levels are still zero, but on the second day and thereafter they again appear to be elevated.

TABLE 8

INFLUENCE OF CORTISONE THERAPY ON BLOOD ACTH CONCENTRATIONS IN PATIENTS WITH RHEUMATIC FEVER

During therapy			*After therapy*		
Pt.	*Day of therapy*	*ACTH (mU/liter)*	*Pt.*	*Day after discontinuing therapy*	*ACTH (mU/liter)*
S.B.	3	7.1	L.A.	1	0
J.B.	10	0	T.F.	1	0
			A.D.	2	6.9
			C.C.	3	7.7
			A.W.	4	0
			T.L.	8	5.2
			L.A.	8	2.9

Similar suppression of circulating ACTH levels during cortisone therapy has been reported previously in patients with congenital adrenal hyperplasia.[166] With this condition, as in patients with rheumatic fever, the circulating ACTH levels are high in the untreated patient and the 17-hydroxycorticosteroid concentrations are simultaneously low. During therapy with cortisone in patients with congenital adrenal hyper-

plasia, 17-hydroxycorticosteroid concentrations are increased and ACTH concentrations decreased to zero; following discontinuation of cortisone therapy, the hormone pattern returns to its original status. This pattern of response to cortisone therapy is in conformity with the postulation that the pituitary release of ACTH is influenced by the circulating concentration of adrenal steroids. According to this theory, when the circulating steroid level becomes elevated, pituitary release of ACTH is inhibited. If this is true, it would explain the elevated concentrations of ACTH which occur in adrenalectomized animals and in patients with Addison's disease, congenital adrenal hyperplasia, or rheumatic fever.

The effects of other types of therapy for rheumatic fever, including ACTH and salicylates, on blood ACTH concentrations are under investigation. However, data are too meager at this time to permit interpretation.

INDIVIDUALIZATION OF HORMONE THERAPY

Since the initial report by Hench and associates[132] on the beneficial effects of cortisone in rheumatic fever, numerous controversial reports have appeared concerning the relative effectiveness of hormonal agents and salicylates in this disease. While there is general agreement that these agents produce more or less prompt subsidence of acute rheumatic symptomatology, the opinion that they do not alter the frequency of cardiac residua has been advanced repeatedly. This opinion has been based upon a limited variety of therapeutic regimens, very few of which have been individualized with regard to the patient, the severity of the disease, or the response to therapy. There is little reason to believe that ACTH and cortisone, in contrast to nearly all other medications, can be used entirely empirically with no regard for the response of the condition under treatment. At the outset of this study, the basic premise was assumed that therapy should be individualized with respect to the factors mentioned. In an early stage of the study, it was found that the minimum consistently effective initial dose of ACTH in therapy of acute rheumatic fever was 1 I.U. per pound per day. Patients who received this much or more responded considerably better with regard to acute rheumatic symptomatology than those who received less. On the basis of later studies, it was determined that 1 I.U. of ACTH was roughly equivalent to 3 mg. of cortisone with regard to the influence on circulating steroid concentrations and urinary 17-hydroxycorticosteroid excretion.[249] Therefore, a dose of cortisone of 3 mg. per pound per day was taken as the standard initial cortisone dose in therapy of rheumatic fever.

Nearly all investigators who have studied hormone therapy of rheumatic fever have reported a rapid and rather dramatic effect on the acute manifestations of the disease. In certain studies, considerable variation has been observed from patient to patient regarding the rapidity of this response. Yet, in most studies, the patients have been maintained on a rigid, routine schedule of drug administration, with regard to both dose and duration of therapy.

Since there is considerable variability with which the rheumatic process subsides during hormone therapy and since the clinical criteria of rheumatic activity disappear so rapidly under the influence of hormones, it is difficult to arrive at a satisfactory definition of the proper period of time to continue therapy at the initial maximum dose level. In our experience, the erythrocyte sedimentation rate is not a satisfactory criterion by which to determine the time of tapering and discontinuing hormone dose, since it becomes normal too soon after the initiation of therapy. If hormone therapy is discontinued when the erythrocyte sedimentation rate becomes normal, the patient is likely to exhibit a "clinical rebound."

At certain centers, the C-reactive protein concentration has been used as the criterion to determine the presence or absence of rheumatic activity. This, in our experience, although more reliable than the erythrocyte sedimentation rate, is not a completely satisfactory criterion. Various others of the acute phase substances have been studied in the hope that one would serve as a more reliable indicator of rheumatic activity. Of these, the serum mucoprotein concentration has been found to be the most satisfactory. In a previous report,[105] it was concluded that there was little hazard of clinical rebound if hormone therapy was continued in maximal doses until the serum mucoprotein concentration had decreased to a value less than 6 mg. per cent and if tapering of dose then was carried out slowly and cautiously.

At the present time in our clinic, individualization of therapy is considered an integral and important part of hormone treatment of rheumatic fever. Such individualization is accomplished by (1) adjusting the size of the dose to the size of the patient, that is, 1 I.U. of ACTH or 3 mg. of cortisone per pound of body weight as the minimum initial daily dose; (2) adjust-

ing the size of dose to the severity of illness, severely ill or "critical" patients receiving a larger initial daily dose; and (3) adjusting the duration of therapy according to the response of the patient. Therapy with the full initial dose is continued until the following criteria have been met: (1) no clinical evidence of activity remains; (2) the erythrocyte sedimentation rate has been normal for at least one week; and (3) the serum mucoprotein level has decreased at least to 6 mg. per cent. When these criteria have been fulfilled, the dose is very gradually reduced at two- to three-day intervals. Before each reduction of dose, the erythrocyte sedimentation rate is determined; if there is any evidence of an increasing rate, the dose is not decreased further until this has disappeared. Since this policy has been adopted, we have seen no evidence of clinical rebound in any patient treated.

RESULTS OF HORMONE THERAPY

In view of the evidence presented that patients with rheumatic fever have relative adrenal insufficiency and of the interpretation that this constitutes an indication for hormone therapy, it should be of interest to compare the results of hormone therapy with those of therapy with salicylates and with bed rest alone.

Table 9 indicates the response of acute manifestations of rheumatic fever in a series of patients treated according to the schedule outlined.

TABLE 9

COMPARATIVE EFFECTS OF ACTH, CORTISONE, SALICYLATES, AND BED REST UPON VARIOUS ACUTE MANIFESTATIONS OF RHEUMATIC FEVER

	ACTH Rx	*Cortisone Rx*	*Salicylate Rx*	*Bed Rest*
Joint involvement: mean days until improved	0.7	0.8	1.2	7
Mean days until disappeared	1.7	2	3.3	19.8
Mean days until temperature normal	1.8	1	2	
Mean days until erythrocyte sedimentation rate normal	15.6	11.9	43.4	48.2
S.E.M.	±1.97	±2.2	±5.28	±13.8

The response of patients treated with salicylates or with bed rest is included for comparison. Most of the salicylate-treated subjects received an initial daily dose of approximately 1 gr. per pound of either sodium salicylate or aspirin.

Improvement in joint involvement occurred rapidly in all of the drug-treated patients, with somewhat more rapid improvement occurring in the patients treated with hormones than in those treated with salicylates; joint symptomatology disappeared completely within two days in nearly every hormone-treated patient. In most of the salicylate-treated individuals, disappearance of joint involvement was equally rapid, but in a few patients it was delayed. Thus, the mean time required was somewhat greater for the salicylate-treated than that for the hormone-treated patients. Fever responded very rapidly to each of the drugs used, and there were no real differences among the groups. Return of elevated erythrocyte sedimentation rate to normal was much more rapid in the hormone-treated patients than in those treated with salicylates or bed rest.

TABLE 10

REAPPEARANCE OF SIGNS OR SYMPTOMS OF RHEUMATIC ACTIVITY DURING TAPERING PERIOD OR UPON DISCONTINUATION OF THERAPY

	ACTH (29 patients)	*Cortisone (12 patients)*	*Salicylates (21 patients)*
Arthritis	1	0	6
Arthralgia	1	2	1
Fever	3	4	6
Abnormal erythrocyte sedimentation rate	17	6	8

Table 10 presents data concerning the reappearance of signs or symptoms of rheumatic activity upon tapering or discontinuation of therapy. The only instance of reappearance of arthritis among the hormone-treated patients occurred in a boy who was given ACTH intravenously in what we would now consider to be inadequate doses for an insufficient period of time. This same patient accounts for the only instance of recurrence of arthralgia among the ACTH-treated patients and, in addition, for an instance of recurrence of fever and elevation of erythrocyte sedimentation rate. In contrast to the hormone-treated patients, 6 of the 21 salicylate-treated individuals exhibited a recurrence of arthritis. This occurred repeatedly upon attempts to taper therapy in 3 patients after as long as forty-seven, one hundred, and one hundred-six days of treatment. It is interesting that such clinical evidence of rebound did not occur in the patients treated with ACTH or cortisone.

Reappearance of an elevated erythrocyte sedimentation rate occurred in relatively more of the hormone-treated patients than in those treated with salicylates. However, in all groups, the rate shortly returned to normal without further therapy except in those salicylate-treated patients who had sufficiently severe clinical rebound to make reinstitution of therapy mandatory.

While the effects of the hormones on the

acute manifestations of rheumatic fever are reasonably impressive, they should not be overemphasized, since, if hormone therapy of rheumatic fever is to be of any great value, it must accomplish more than a mere shortening of acute symptomatology of the disease. The most important consideration, and the one most difficult to evaluate, is the effect on cardiac damage resulting from the disease. In an attempt to obtain an objective evaluation of the effects of therapy on the residual cardiac status of the patient, a comparison has been made of the incidence of residual cardiac murmurs in patients who were *known to have no murmur* before the onset of the attack of rheumatic fever (table 11). Of the many patients whom we

TABLE 11

RESIDUAL CARDIAC MURMURS IN 80 CHILDREN AT VARYING INTERVALS FOLLOWING AN ATTACK OF ACUTE RHEUMATIC FEVER

	At time of discharge	*Interval since discharge*				
		3 mo.	*6 mo.*	*1 yr.*	*2 yr.*	*3 yr.*
Hormone-treated	52% (46)	40% (35)	26% (34)	16% (31)	8% (25)	6% (17)
Not treated with hormones	74% (34)	77% (31)	67% (27)	81% (26)	75% (20)	82% (17)

have treated during the past four years, there were 80 who could be included in this group. Of these, 46 were treated with either ACTH or cortisone, 21 were treated with salicylates, and 13 with bed rest. Since no significant difference was found between the ACTH and cortisone groups and between the salicylate and bed-rest groups with regard to cardiac residua, the hormone-treated groups were combined and compared with the groups not treated with hormones in this and the following tables. In table 11, data are presented concerning the percentage of patients who had any detectable residual cardiac murmurs at various follow-up periods. The numbers in parentheses refer to the number of patients upon which these percentages are based.

At the time of institution of therapy, all of the hormone-treated patients and all but 1 of those not treated with hormones had murmurs. At the time of discharge from the hospital, 52 per cent of the hormone-treated patients and 74 per cent of those not treated with hormones had residual cardiac murmurs. Thereafter, there was no significant change with time in the incidence of residual murmurs in the group not receiving hormones, whereas in the hormone group the incidence of residual murmurs decreased with each successive examination until at one year only 5 of 31 patients (16 per cent) had any residual murmur. In the groups of patients who were followed for two and three years, only 8 and 6 per cent, respectively, had murmurs. The figure of 6 per cent with a residual murmur at three years after hormone therapy represents only 1 of 17 patients; this patient had a grade I mitral systolic murmur after hormone therapy which had been present consistently since his acute illness. Of the remaining 4 patients who had murmurs at one year, the murmur had disappeared in 2 who were examined a year later; the remaining 2 patients were lost to follow-up.

The difference between the 2 groups with regard to cardiac residua cannot be attributed to patients lost to follow-up; approximately 30 per cent of the hormone-treated patients for whom complete follow-up data are not available had murmurs at their latest examination, while approximately 80 per cent of the patients not treated with hormones without complete follow-up data had murmurs at their latest examinations. Moreover, a greater proportion of the patients in the hormone groups for whom follow-up data are not complete were last examined early during the follow-up period, at a time when the incidence of murmurs among the other hormone-treated patients was highest; relatively more of the patients not treated with hormones were lost late in the follow-up period. Follow-up data are included at each period for all patients except those who (1) were not available for examination, (2) had not yet reached the indicated interval following discharge from the hospital, or (3) had suffered a new attack of rheumatic fever since the preceding follow-up period. In each therapy group, follow-up was terminated at the time of recurrence in any patient who developed a new attack.

Table 12 shows the number of patients who developed new cardiac murmurs at varying intervals following discharge from the hospital. The figures refer to the number of patients who developed any murmurs not audible at the immediately preceding follow-up period. The figures in parentheses refer to the number of patients included in each follow-up period.

TABLE 12

APPEARANCE OF NEW MURMURS FOLLOWING DISCHARGE

	Interval since discharge					*Total number of new murmurs*
	3 mo.	*6 mo.*	*1 yr.*	*2 yr.*	*3 yr.*	
Hormone-treated	2 (35)	0 (34)	1 (31)	1 (25)	0 (17)	4
Not treated with hormones	4 (31)	3 (27)	4 (26)	4 (20)	3 (17)	18

Among the hormone-treated patients, 2 were found at three months to have murmurs which had not been audible at the time of discharge. An additional patient developed a new murmur at the one-year follow-up and 1 at the two-year follow-up period. Of these 4 new murmurs, 3 disappeared within one year; only two months have elapsed since the fourth was discovered. In contrast to the hormone-treated patients, those treated with salicylates or bed rest were found to have developed new murmurs much more frequently, and in this group new murmurs appeared at each follow-up period. These murmurs did not seem to be transient; of the 18 new murmurs which were noted, 9 were known to persist for at least two years. Follow-up data are not available at the two-year interval for the remaining 9 patients.

Table 13 presents similar data but considers only the new appearance of diastolic murmurs and of systolic murmurs of grade II or greater intensity. No such murmurs had their first appearance following discharge among the hormone-treated patients. In contrast, new diastolic murmurs appeared in 6 of the patients not treated with hormones; 4 of these murmurs were known to persist for two years. In 1 patient, the murmur disappeared within one year; 1 patient died nine months after the first appearance of the murmur. New systolic murmurs of grade II or greater intensity appeared in 7 of the patients not treated with hormones; these murmurs were known to have persisted for two years in 4 patients and no data are available concerning the remaining 3 patients.

TABLE 13

APPEARANCE OF NEW DIASTOLIC MURMURS OR SYSTOLIC MURMURS OF GRADE II OR GREATER INTENSITY FOLLOWING DISCHARGE

		Interval since discharge					*Total number of new murmurs*
		3 mo.	*6 mo.*	*1 yr.*	*2 yr.*	*3 yr.*	
Hormone-treated	Diastolic	0	0	0	0	0	0
	Systolic	0	0	0	0	0	0
	Number examined	35	34	31	25	17	
Not treated with hormones	Diastolic	0	2	1	2	1	6
	Systolic	2	0	2	2	1	7
	Number examined	31	27	26	20	17	

A large number of reports concerned with the use of ACTH and cortisone in rheumatic fever have expressed pessimism with regard to the prevention of permanent cardiac damage. These views are not supported by the observations of the present study. The extremely small percentage of hormone-treated patients who were found to have residual cardiac murmurs through follow-up periods of up to three and three-fourths years and the infrequent appearance of new murmurs after discontinuance of therapy in these individuals are encouraging indeed. The effects of hormone therapy of recurrent and chronic rheumatic fever have been reported elsewhere and likewise have been encouraging. Observations of each of these studies suggest that the rheumatic process may be terminated by ACTH or cortisone, with prevention of permanent cardiac residua.

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Infants over 2 weeks of age with obstructive jaundice and alcoholic stools of nonmedical causation are amenable to surgery often enough to make such intervention worthwhile. Relief may be effected in nearly one-third of cases, find E. M. Greaney, M.D., W. H. Snyder, Jr., M.D., and Lawrence Chaffin, M.D., of the Los Angeles Children's Hospital and University of Southern California, Los Angeles. The method recommended comprises exposure through a transverse incision, on-the-table cholangiography when feasible, and complete dissection of the portal triad. If the cholangiogram shows a normal extrahepatic ductal system, exploration is abandoned.

E. M. Greaney, W. H. Snyder, Jr., and Lawrence Chaffin: Am. J. Surg. 88:17-22, 1954.

Postoperative Use of Levo Dromoran Tartrate

RICHARD C. GAARD, M.D.
Minneapolis, Minnesota

Although numerous reports in the literature relate to the use of racemic Dromoran hydrobromide and Levo Dromoran Tartrate for the relief of pain, to the best of our knowledge no published report has appeared on the use of either of these materials in the recovery room during the immediate postoperative period. The depressant drugs used during the operative procedure tend to bring about a state in the recovery room in which the hypnotic effects have been dissipated but in which sufficient amounts of the drugs remain in the circulation to exert an additive or synergistic effect on any drugs given for the relief of pain or restlessness.

This persistence of potential drug effects is particularly true when Pentothal is employed. We have in the past used morphine and other opiates in the recovery room with unsatisfactory results because the patients became depressed and sometimes suffered respiratory embarrassment. In view of these considerations, the present study was established to investigate the possible usefulness of Levo Dromoran Tartrate as a substitute for morphine in the recovery room.

METHODS

In this program 100 postoperative patients were studied. No special effort was made to select patients on the basis of age, operative procedure, and so forth. Instructions were given the nurses in the recovery room relating to the dosage of Levo Dromoran Tartrate which was almost always given by hypodermic. Special forms were provided so that careful records could be kept of time, blood pressure, pulse, respiratory rate, and so on.

The patients were divided into 3 categories according to age: Group A – 2 to 10 years inclusive; group B – 11 to 49 years inclusive; and group C – 51 to 77 years inclusive. Tonsillectomy or appendectomy was performed on 96 per cent of the cases in group A. Major surgical procedures were performed on 81 per cent of the cases in group B and on 90 per cent of group C. Group A usually received Pentothal induction with endotracheal ether-oxygen, whereas B and C generally received Pentothal, curare, and nitrous oxide or ether.

RESULTS

Table 1 summarizes the data obtained in this series. The total number of cases in each group shows a preponderance of group A. This is the group that is perhaps the greatest problem in the recovery room because these children cannot adequately express pain relief nor can they make the necessary adjustment to the presence of pain. In addition, there is always the feeling of urgency to return the child to the floor so that the anxious parents can be reassured.

The dose employed in each group indicates that in the extreme age groups the requirement for Levo Dromoran Tartrate is decreased. In general, the dosage used in this study is less than that commonly employed for the relief of pain. A total of 109 doses was given; 2 doses were administered intravenously, 1 intramuscularly, and the remainder subcutaneously.

An attempt was made to quantitate the analgesic and sedative effects by establishing a code

TABLE 1
USE OF LEVO DROMORAN TARTRATE IN RECOVERY ROOM

	Group A	*Group B*	*Group C*
Age range (yrs.)	2–10	11–49	51–77
Average age (yrs.)	5.8	34.3	64.0
Males	33	10	9
Females	16	21	11
Total number cases	49	31	20
Total number doses	51	33	25
Dose range (mg.)	0.25–1.0	1.0–2.0	0.5–2.0
Average dose (mg.)	0.56	1.3	1.1
Average analgesia per dose	—	1.7	1.3
Average sedation per dose	1.9	1.5	1.4
Number cases quieted	33	5	5
Number cases sleep	7	1	0

RICHARD C. GAARD, *a 1945 graduate of the University of Minnesota Medical School, is director of the department of anesthesiology at Fairview Hospital, Minneapolis.*

as follows: 0 – no effect; 1 – slight; 2 – moderate; and 3 – marked. The degree of analgesia in group A was impossible to measure because the child's response was not dependable. An indirect evaluation of the relief of pain in this group can be obtained from the amount of sedation or hypnosis which was observed. To a lesser extent the analgesia in groups B and C was difficult to evaluate properly because these patients were still under the influence of other drugs given in the operating room. Indirect measurement could be made in all 3 groups by the return of pulse and blood pressure to normal and stabilized readings.

Our goal with reference to sedation was to obtain a degree somewhere between slight to moderate (1.5). Pronounced sedation (3) was as undesirable in our eyes as no sedation at all (0). That this goal was achieved in the course of this experiment is shown by the average figures for each group calculated on a dose basis. The children in group A were much more prone to sleep than the subjects in groups B and C. The restlessness and crying which are so characteristic of children were abated in 40 instances of a total of 49 patients. In all cases these children could be aroused readily and responded to stimuli. The rapid pulse and respiratory rates which characterize pain in adults decreased markedly in groups B and C.

DISCUSSION

The great variety of agents commonly employed during surgery to provide effects such as anesthesia, analgesia, hypnosis, and muscular relaxation, complicates the problem of drug therapy in the recovery room. Although the major effects of drugs given during surgery are dissipated, significant amounts remain in the circulation to exert a pharmacologic effect. One purpose of a recovery room is to prepare the patient for return to the floor. Therefore, in spite of the presence of depressing drugs in the circulation, the patient must leave the recovery room with stabilized vital functions, adequate analgesia, and sedation.

During the immediate postoperative period, Levo Dromoran Tartrate, in our experience, has proved to be the most satisfactory of the opiates on the basis of safety and effectiveness. In the dosage used, the desired degree of analgesia and sedation was provided without depression or respiratory embarrassment.

SUMMARY

1. Levo Dromoran Tartrate was administered to 100 patients in the recovery room during the immediate postoperative period.

2. The desired degree of analgesia, sedation, and stabilized vital functions were obtained without causing the occurrence of undesirable side effects.

3. Levo Dromoran Tartrate was particularly effective in children.

The generous assistance of Eleanor Oseth, R.N., Barbara Sachariason, R.N., Ruth Lett, R.N., Jeanette Christenson, R.N., Dorothy Wiechet, R.N., and Audrey Dorn, R.N. is gratefully acknowledged.

AIR CONDITIONING greatly diminishes contamination in operating rooms. C. R. Edwards, M.D., C. W. McGrady, Jr., M.D., and Audrey M. Funk of the University of Maryland, Baltimore, found that the bacterial count decreased 53 per cent after air conditioning and believe that even greater reduction can be achieved by use of specially designed fiber filters or electrical precipitation elements. Anaerobic organisms were not found in cultures either before or after conditioning.

C. R. EDWARDS, C. W. MCGRADY, JR., and AUDREY M. FUNK: Am. Surgeon 21:189-194, 1955.

Lancet CLINICAL REVIEWS

This department of The Journal-Lancet *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Hypertensive and Coronary Heart Disease Complicated by Pernicious Anemia

JOHN F. BRIGGS, M.D.

St. Paul, Minnesota

A well-known fact for years has been that an individual may suffer from a chronic disease, but, by virtue of his ability to adapt and adjust to the disease and accept limitations placed upon him by his illness, he may carry on a normal or nearly normal life. The appearance, however, of some secondary disease may exert such influence upon the chronic illness that the patient is precipitated into invalidism. Frequently, the new illness may be of such character that it can be benefited by treatment or even cured by specific forms of therapy. In this instance, the additive effect of the secondary illness is canceled and, by virtue of the treatment, the patient is returned to his previous state of health.

Victims of cardiovascular disease are frequently able to carry on a useful, social, and economic life. The development, however, in these patients of another disease either acting directly upon the cardiovascular system or expressing itself through this system or by placing an extra burden upon it can produce severe cardiac disability resulting in invalidism. Should the new illness be of a curable or reversible nature, then treatment directed toward this condition removes the burden from the cardiovascular system and the patient then enjoys the same degree of health that he had before the advent of the new disease. Failure to recognize the influence of other diseases upon a previously damaged heart has frequently led to unnecessary invalidism and often death. If the role of these complicating diseases and their influence upon the cardiovascular system are recognized, particularly when such an illness is curable or reversible, proper treatment will restore the patient to his previous degree of compensation.

In support of this statement the following case is presented: Mr. H. B., a white, married, 56-year-old farmer was first seen on October 7, 1953 with the story that in 1951, after a severe upper respiratory infection, he noticed a pain over the sternum which radiated into his left arm and hand. This pain occurred whenever he was pitching bales of hay or lifting heavy articles. When he stopped work and rested for a few minutes, the pain disappeared. Later he noticed that if he ate a large meal before doing his farm chores or walked any distance, the pain occurred more often and with greater severity. He soon learned that if he rested an hour or two after eating, he then could carry on his usual activities without pain. After a few months the pain disappeared almost completely and he was relatively free from this distress until one year before he consulted a physician. In the early part of the summer of 1953, while doing chores he noticed that the pain came with greater frequency and with more severity. It was now associated with a feeling of tightness and constriction around his chest and, at the same time, he encountered some difficulty in breathing. The pain always radiated down the left arm, forearm, into the wrist, and was associated with a numb feeling in his fingers. Rest no longer easily relieved it. The condition gradually worsened until he was unable to carry on his usual farm work; weakness appeared and he found that he had to rest most of the time. His family physician observed that he experienced relief by the use of nitroglycerin and also by the use of whiskey. The patient noticed that during the winter and cold days the pain became worse and that he had less reserve than previously. The condi-

John F. Briggs, *a 1929 graduate of the University of Minnesota Medical School, is clinical assistant professor of medicine at the University of Minnesota.*

tion became so severe that he found he ultimately was unable to carry on any of his customary activities.

The family history was negative with exception of the fact that his mother had suffered from pernicious anemia and a brother was victim of the same illness.

Physical examination revealed a chronically ill appearing white male, 5 ft. 9¾ in. tall, weighing 197 lb. The physical examination was completely negative with the exception of a contact dermatitis of his right foot, atrophic testes, and emphysema. Blood pressure was 168 110, pulse 72, and temperature 98.6° F.

Laboratory work showed urine negative, blood sugar 80 mg., urea nitrogen 19 mg., the blood chloride 626 mg., basal metabolism plus 20 per cent, hemoglobin 9.4 gm., the red count 2,220,000, the white count 5,400, the neutrophils 66 per cent, lymphocytes 28 per cent, eosinophils 6 per cent, sedimentation rate was 54 mm. in one hour, the platelet count 306,000, and the agglutination test for undulant fever was negative. Gastric analysis revealed no free hydrochloric acid and stool examinations were negative. Blood potassium was 18 mg. or 4.6 mEq. and the sodium was 327 mg. or 142 mEq. The icterus index was 10 units. The study of the blood smears revealed anisocytosis, hypersegmented polymorphonuclear cells, and poikilocytosis. The chest x-ray was normal, and x-ray examination of the gastrointestinal tract was normal. The x-ray film examination of the gallbladder was normal. The electrocardiograms revealed an abnormality with negative T waves in lead 1, negative T 4, and negative T in leads V_2 and V_3. A sternal bone marrow study showed a megaloblastic bone marrow consistent with the diagnosis of pernicious anemia.

It was concluded that the patient suffered from hypertensive heart disease with coronary insufficiency and pernicious anemia. Symptomatic treatment to relieve the coronary insufficiency was started and immediate efforts were directed toward correcting the severe anemia. After the use of intramuscular liver, a reticulocyte response of 9 per cent was obtained and a rapid rise occurred until the hemoglobin reached 13.3 gm., the red count 3,420,000, and the white count 8,500. With the return of the blood picture to normal, the electrocardiogram returned to near normal limits. Since then he has had few attacks of coronary pain, and has maintained his blood picture with a hemoglobin of 95 per cent. He has had no further severe attacks of pain and has been able to resume and actively engage in his farm activities with only moderate limitation in his work.

SUMMARY

The case presented represents an individual who had hypertensive heart disease. For years he was not disabled by virtue of the affliction and was able to carry on his usual activities. After an episode of an upper respiratory infection in 1951, for a short period of time he had evidences of coronary insufficiency. These seizures practically disappeared for a year, when they again reappeared. The pain gradually worsened in character until finally he became totally disabled because of the coronary heart pain. At first rest, nitroglycerin, and whiskey provided relief. Finally the usual measures to relieve the pain failed completely. On examination, in addition to hypertension and coronary insufficiency, he was found to have pernicious anemia with a rather severe degree of anemia. It is well known that coronary insufficiency pain can be produced in individuals who are anemic. As a result of the decreased oxygen carrying capacity of the blood, insufficient oxygen is brought to the myocardium, and as a result the typical pain of coronary insufficiency appears. In this instance, we believe that the combination of a mild coronary sclerosis was precipitated into a severe disability by virtue of the associated anemia. Treatment directed to the anemia resulted in the return of the blood to normal and has enabled him to resume a practically normal life.

In conclusion, a case has been reported of an individual suffering from hypertension with coronary heart disease who was precipitated into severe cardiac embarrassment and total disability by virtue of an associated pernicious anemia. Treatment directed toward the reversible disease, namely, pernicious anemia, resulted in a complete disappearance of the disability and the return of the patient to a nearly normal, active, and productive life.

Lancet Editorial

The Meaning of Social Medicine

Because of the revolutionary ideas and principles set forth by Dr. Galdston, his book will be treated by the reviewer as an editorial rather than a book review.

In his scholarly and thought-provoking monograph, Dr. Galdston devoted 120 pages to the origin, growth, and historic significance of a new ideal and philosophy of modern medicine.

Since social medicine carries different meanings to different men, he believes that to venture a precise definition of the term would be futile.

In order to understand the meaning better, of first importance is a definition of what it is not. Social medicine is not synonymous with socialized medicine as many believe. It is the accumulation of all the knowledge gained from the time of Hippocrates from all the biologic, physical, and social sciences. It is the grand offspring not only of clinical medicine but of all environmental influences, living and nonliving, which are relevant to health and disease. Just as anatomic pathology is the parent of clinical medicine, by the same token, social pathology conceived and gave birth to social medicine. It embraces clinical medicine, preventive and public health, mass as well as individual psychology, health as well as disease, and etiology as well as diagnosis.

On the other hand, socialized medicine is a political and social system of "the application of medical economics, of organizational programs for the distribution of medical services." It is the inevitable result of the revolutionary social, economic, political, and humanitarian changes in society.

Limited state medicine or government medicine has been steadily encroaching upon the territory of private medicine not because of the edicts of any political party but because of the disaffection with health "potentials not fully realized" and because of the "mounting awareness that a relatively large portion of the population suffers from many unmet needs for medical services."

Why has social medicine been advanced as a new and different discipline? The author courageously gives as a dominant reason the failure of modern medicine. He hurries to his defense by admitting the brilliant triumphs of curative medicine, while presenting indisputable statistical proof of his contention that the fame of modern medicine rests "upon a Pyrrhic victory." Although medicine has achieved miracles in the treatment of diseases and the prevention of specific diseases, Dr. Galdston presents statistical evidence to show it has "failed in the elimination of disease and in the promotion of health."

On the credit side, using New York City as an example, he reveals the pronounced decrease in over-all mortality rates in the past fifty years. On the debit side, however, he shows the pronounced increase in both the mortality and morbidity of the chronic and degenerative diseases. Whereas the infectious diseases were the chief killers, especially of children in 1900, today cancer and cardiovascular diseases have usurped the front ranks. Medical science has made "infinitely more progress in the combat against man's external enemies, for example, bacteria, viruses, and so forth, than in the understanding and amelioration of man's internal milieu." Although vaccines, sera, antibiotics, and so on, have accomplished curative miracles against some diseases, the author contends that these agents do not and cannot of themselves promote and maintain health and well being. In other words, modern medicine has in a large measure converted mortality into morbidity.

If we are ready to accept the author's evidence as credible and his polemics as logical, the question to be asked at this point is, What is wrong with medical education? The author affirms that the medical curriculum of today is fundamentally irreconcilable with social medicine. He believes the goals and objectives of medical education have not changed much since the days of Sydenham. Today the student is taught primarily to recognize the presence of disease, fit a diagnosis into some nosological category, and treat the disease or the diseased person so that the disease is eliminated. Dr. Galdston believes clinical and preventive medicine should be absorbed into what he considers is the broader concept of social medicine. He would reveal medicine as a "fascinating panorama of the adventure of living." The student would be trained to recognize when an individual is failing in achievement and performance and to learn "to unravel and identify the complex factors which impede or divert the

growth, development or function of the individual." The orientation of the student would be radically altered. Effort would be made to determine and correct that "which impedes the individual in the fulfillment of his adventure in living." He would then proceed to prepare the person for a continuously efficient and healthy life. All this Dr. Galdston has named "Eubiotic" medicine, that is, medicine dedicated to helping the individual fulfill his greatest potentialities.

Granting that social medicine is not merely a Utopian dream but offers a logical and practical resolution of the multiplex problems which now beset society and medicine, the reviewer does not foresee that medical schools will make such a radical change in their curriculum.

Whether or not one agrees with the author's polemics, this book is recommended for every student and physician and to every thoughtful person who cares to form an opinion on the social implications of medicine.

MAX SEHAM, M.D.

The Meaning of Socialized Medicine, by IAGO GALDSTON, M.D., 1954. Cambridge, Massachusetts: Harvard University Press. $2.75.

The Foundations of Surgery, by GEORGE PERKINS, 1954. Edinburg: E. & S. Livingstone. $3.00.

This is a small text on physical diagnosis. The book is easy to read with a large quantity of material expressed in a few words.

However, some of the statements are misleading. On page 49, regarding recurrent hemorrhage, the author states, " . . . the rising blood pressure sweeps out the clot that is occluding the opening and bleeding starts again." Any retarded or recurrent hemorrhage is more apt to be related to poor clot formation and retraction, and also the muscular contractions of the organ involved rather than the corrected blood pressure. On page 90, it is stated that "whenever the total proteins in the plasma drops below 5-gm. per cent, and the albumin drops below 2.5-gm. per cent, there is universal edema." It is generally known that edema is largely related to tissue elasticity and pressure rather than to low plasma proteins.

The contents of the book are well written and the author adequately covers a large subject in a few pages.

DONALD S. AMATUZIO, M.D.

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The Clinical Significance of Disturbances in the Delivery of Sweat, by MARION B. SULZBERGER, M.D., and FRANZ HERMANN, M.D., 1954. Springfield, Illinois: Charles C Thomas. 212 pages. $6.75.

This is an excellent monograph pertaining to certain investigative studies on the physiology of sweating, and on the pathologic disturbances and treatment of these disorders. The book is divided into 3 sections. The first concerns the various methods and technics employed in the study of "sensible" and "insensible" perspiration together with discussions of the results of these studies. In the second section, the authors have classified the various sweat disturbances into 3 general groups: 1. Hyperhidriosis, 2. Hypohidrosis, and 3. Dyshidrosis. The first 2 categories, as the titles indicate, deal with disorders which are characterized by quantitative differences in the amounts of sweat delivery. The third category consists of all the other sweat disturbances, including those characterized by abnormal quality. The etiology, pathogenesis, mechanisms, clinical findings, and applications of the various sweat disturbances are discussed in detail in this section. The third portion of the book is devoted to therapeutic considerations, including both systemic and local measures. This monograph is well written and contains a large amount of useful information. It is of particular interest not only to students of dermatology and those interested in this type of fundamental research, but also to clinicians dealing with these conditions.

ELMER H. HILL, M.D.

Pediatric Diagnosis, by MORRIS GREEN, M.D., and JULIUS B. RICHMOND, M.D., 1954. Philadelphia: W. B. Saunders Co. 436 pages. $10.00.

This book can be of great interest to every young physician starting out in the field of pediatrics or every general practitioner who wants to improve his diagnostic ability in this field. Of particular interest is the chapter on the neurologic examination of the child. But excellent chapters on examinations of all parts of the child's body are included. The reader will find useful tables on the weight and height of children of different ages and the index is good.

WALTER C. ALVAREZ, M.D.

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Hematology, by CYRUS C. STURGIS, M.D., 1955. Springfield, Illinois: Charles C Thomas. Second edition. 1,222 pages. $19.75.

This second edition contains much material on the significant advances in the field of hematology that have occurred since the first edition was published seven years ago. These advances include: the isolation and identification of vitamin B_{12} and its role in pernicious anemia; the introduction of the folic acid antagonists in the treatment of leukemia and allied conditions; the use of ACTH and cortisone in hematologic disorders; and the importance of drugs used in current therapeutic regimens as etiologic agents in aplastic anemias and agranulocytosis.

Although this edition has been extensively revised, it retains the same basic and detailed historic approach to the subject matter as was used in the previous volume. The

(Continued on page 30A)

Section on PAIN

Comments concerning this Section, criticisms, or suggestions for papers will be most welcome. Physicians are cordially invited to submit articles pertaining to pain for consideration. All inquiries and manuscripts should be sent to Dr. John S. Lundy, 102 Second Avenue Southwest, Rochester, Minnesota, or to the Editorial Department, THE JOURNAL-LANCET, *84 South Tenth Street, Minneapolis, Minnesota.*

Radicular Pain

Including the Guillain-Barre Syndrome*

JOE R. BROWN, M.D.

Rochester, Minnesota

PAIN forms one of the most frequent diagnostic problems a physician faces. It is well known that pain may originate in the viscera, in various musculoskeletal structures, in blood vessels, in peripheral nerves, and within the central nervous sytem. Pain may be located in the organ of source or may be referred to more or less distant structures. Emotional factors may play an important role in the production, severity, and complaint of pain. These few comments are intended to illustrate the importance of determining as accurately as possible the primary source of pain. Attention to specific points in the history and examination often lead to more accurate diagnosis and consequently to more satisfactory treatment.

It is hoped that a specific discussion of certain features of a particular type of discomfort, namely radicular pain, will be of value. The technics of evaluation, the anatomic information, and the clinical observations are all a part of the general armamentarium of a neurologist. For this reason, only one reference to the literature on the subject will be made.

Radicular pain may be defined as pain originating in a nerve root. Because of certain anatomic factors, radicular pain has peculiar characteristics that help differentiate it from pain originating in such locations as viscera, musculoskeletal structures, or peripheral nerves. These characteristics of diagnostic value relate to the distribution of the pain, the type and distribution of associated signs and symptoms, and the factors that intensify or relieve the pain. In some instances, the source of pain may remain obscure, particularly if the pattern of pain is not fully developed, if the history is obscure, or if a satisfactory examination is not possible.

SYMPTOMS

The chief symptoms of lesions of the nerve root are pain and paresthesia. The pain may be described as aching, boring, burning, lancinating, or shooting. The paresthesia is variously described as prickling, tingling, numbness, a feeling that the part is dead or asleep, or the sensation of a tight band. The patient may complain of hyperesthesia and painful distortion of sensation when certain regions of the skin are touched lightly, stimulated by a pin, or contacted by warm or cool objects. Similar regions of skin may be hypesthetic or anesthetic to superficial stimuli. When present, hypesthesia tends to affect all three modalities of superficial sensation relatively equally. Deep sensibility is generally preserved if only one root is involved. Some minor inequalities in superficial sensation may exist due to the region involved. For example, touch by cotton normally is not felt as well in regions of skin that are free of hair, and pinprick is appreciated less on calloused hands. The most reliable information often is gained

JOE R. BROWN, *a 1937 graduate of the State University of Iowa College of Medicine, is with the section of neurology at the Mayo Clinic and is associate professor of neurology in the Mayo Foundation.*

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by testing the appreciation of temperature. In addition to the sensory symptoms just mentioned, motor weakness together with atrophy, fasciculation, and fibrillation of the muscles and reduced muscle-stretch reflexes may occur. Finally, disturbances of sympathetic nerve fibers may produce vasomotor or trophic changes or disturbances in sweating.

Distribution of symptoms. The distribution of symptoms in radicular lesions follows a nerve-root pattern. Some variation occurs among different persons, but, in most instances, the sensory and motor supply of a particular nerve root is reasonably constant. Selected characteristic patterns of distribution will be described. In many instances, the symptoms and findings may be limited to a rather small portion of the total area supplied by an affected nerve. Often the pain tends to be more widespread in the proximal portion of the distribution of the nerve and to be more narrowly limited peripherally. Paresthesia is generally most prominent in the peripheral regions supplied by the nerve root. Referred pains and pains originating in peripheral nerves may follow patterns resembling those of root pain, but careful delineation of the distribution of the pain often clarifies its source.

Effect of cough, sneeze, and strain. The effect produced by coughing, sneezing, or straining is often diagnostic of radicular pain. A rapid increase of intrathoracic or intraabdominal pressure by coughing, sneezing, straining at stool, or lifting of heavy objects may be expected to initiate or intensify radicular pain. The increase in pressure is transmitted by the vena cava to the veins of the intervertebral foramina and thence to the venous plexus of the epidural space. The resultant distention of the epidural veins compresses the dura toward the spinal cord and places traction on the nerve roots, which are relatively fixed at the intervertebral foramina. The mechanism of this increase in root pain was described by Eaton,[1] who noted the narrowing of a column of ethyl iodophenylundecylate (Pantopaque) in the subarachnoid space when the patient rapidly increased his intrathoracic or intraabdominal pressure. Under normal circumstances, the traction on nerve roots is not sufficient to produce pain. However, in the presence of inflammatory or compressing lesions of nerve roots, the pain is initiated or accentuated.

Nocturnal aggravation of pain. Increase of pain at night is frequently an indication of radicular origin. The pain characteristically awakens the patient any time from 2 to 4 A. M. and is relieved by walking. Some patients may be able to sleep only by sitting in a chair all night. Nocturnal pain of root origin is produced by traction on the involved nerve root due to an increase in the length of the body when the patient assumes a recumbent position. This gain in length is due to an increase in the space occupied by the intervertebral disks and occurs most rapidly during the first hours of sleep. Because the spinal cord is fixed at the foramen magnum by its continuity with the brain stem, any increase in length of the body produces traction on the nerve roots at the intervertebral foramina. Because much of the nocturnal gain in bodily length is lost rapidly when the patient assumes an upright position, nocturnal pain of root origin tends to subside after fifteen to thirty minutes in an upright position.

Effect of jugular compression. Jugular compression may increase the root pain, particularly when the pain is due to tumors or other relatively large mass lesions. Compression of the jugular veins in the neck produces an increase in intracranial pressure, which is transmitted to the spinal subarachnoid space. This transmitted pressure tends to displace the mass and accentuate the pain. Jugular compression usually does not increase the pain in small lesions limited to a nerve root and does not always increase the pain from a larger mass lesion. Hence, it is a sign that is less often useful than some others.

Effect of stretching nerve roots. Stretching of the nerve root produces or increases pain due to a radicular lesion. Since the nerve roots are relatively fixed at the intervertebral foramina by the dural sleeve and since the spinal cord is continuous with the brain stem at the foramen magnum, flexion of the neck to bring the chin on the thorax accentuates root pain. Stretching peripheral nerves by raising the straightened leg or by bending the trunk forward with the knees straight similarly tugs on nerve roots and intensifies root pain. The maneuver of simultaneous forward bending, flexing the neck with the chin on the thorax, and giving a hearty cough reinforces the traction on nerve roots. Results of this reinforcement test often are positive when results of other tests for the intensification of root pain are normal. In general, these tests are more effective and easier to interpret when the lesion is in the lumbar region than when in the cervical or thoracic region. Pain originating in the thoracic wall or from the pleurae is increased by coughing and sneezing, which renders these signs less valid when the lesion is

in the thoracic region. There is no practical way of tugging on nerve roots by stretching the intercostal nerves. It should be noted that pain originating from peripheral nerves or plexuses is intensified by stretching the peripheral nerves.

Compression of the nerve root. Pressure on the nerve at the intervertebral foramen also accentuates radicular pain. The intervertebral foramina of the cervical portion of the spinal column may be narrowed by extension of the neck and by rotation or lateral flexion toward the affected side. Lateral flexion while the neck is in extension produces even greater compression of an affected nerve root. In the lumbar region, similar effects also may be produced by extension, lateral flexion, and rotation of the lower part of the back. The "anvil test" also may intensify root pain by compression at the intervertebral foramen. While the patient is seated, the examiner places one hand, palm down, on top of the patient's head and then strikes the hand sharply with his other fist. Generally the patient should be warned before this test is performed lest he misunderstand. Direct fist percussion of the patient's vertex without interposition of the examiner's hand as a buffer tends to divert too much of the patient's attention to the top of his head and interferes with adequate interpretation of the test. Direct steady downward pressure on the head of a sitting patient also may accentuate root pain. Relief of pain by upward manual traction on the neck or downward traction on the pelvis may be a useful dignostic sign.

RELATIONSHIP OF SYMPTOMS TO DISTRIBUTION OF NERVE ROOTS

The characteristic distribution of nerve roots affords a useful diagnostic aid. As already indicated, variations occur in the anatomic distribution in different persons, and variations may be present in the number of vertebrae in particular segments of the vertebral column. Also, a lesion may not be limited to one nerve root but may involve multiple roots or may involve the spinal cord or a nerve plexus in addition to a nerve root. Further, the symptoms may be atypical or incompletely developed, and some patients are not adept at observing and describing their symptoms. All these factors interpose difficulties in deciding which root is involved. However, the following are the usually encountered patterns of distribution of nerve roots.

1. Cervical-nerves 1 and 2 are distributed over the occiput toward the vertex, while cervical-nerve 3 covers the nuchal area and the ear.

2. The dermatome of cervical-nerve 4 is limited to the neck, while that of cervical-nerve 5 extends from the neck to the shoulder and down the lateral aspect of the upper portion of the arm.

3. With lesions of cervical-nerve 6, the pain extends from the neck to the posterior aspect of the trapezius muscle and upper part of the scapula, down the dorsolateral aspect of the arm, and the radial aspect of the forearm and into the thumb. Paresthesia is usually felt in the thumb. The biceps reflex may be reduced.

4. Symptoms of lesions of cervical-nerve 7 follow the same general distribution, except that the pain and paresthesia are in the middle and index fingers. The triceps reflex may be reduced.

5. The pain in lesions of cervical-nerve 8 tends to involve the scapular and the pectoral regions. This pain extends down the inner aspect of the arm and the ulnar aspect of the forearm into the little finger. The paresthesia involves the little finger.

6. Characteristic patterns associated with certain key thoracic and upper lumbar nerves act as landmarks for the general distribution in these regions. Pain from involvement of thoracic-nerve 4 extends to the nipple line, whereas pain originating in thoracic-nerve 7 goes to the xyphoid, that in thoracic-nerve 10 to the umbilicus, and that in lumbar-nerve 1 to the groin.

7. Pain in lesions of lumbar-nerve 3 generally extends from the upper lateral part of the thigh anteriorly across the midthigh and downward to the medial aspect of the knee.

8. Pain originating in lumbar-nerve 4 usually follows a course down the posterolateral aspect of the thigh and the anterolateral part of the leg, stopping before the ankle is reached. The quadriceps reflex may be reduced.

9. Beginning in the buttocks, pain in lesions of lumbar-nerve 5 extends down the posterior part of the thigh, the posterolateral portion of the calf, the lateral aspect of the ankle, and the dorsum of the foot to the great toe. Paresthesia may be felt in the great toe and the gastrocnemius-soleus reflex may be reduced.

10. Pain originating in sacral-nerve 1 follows a similar pattern except terminally, where the extension is along the lateral aspect of the foot to the little toe. The gastrocnemius-soleus reflex may be reduced, and numbness and tingling may be present in the little toe.

11. The lower sacral and coccygeal roots project to the buttocks, posterior aspects of the thighs, and the perineum.

NERVE ROOTS AND VERTEBRAL SEGMENTS

The location of nerve roots in relation to the vertebral segments is of importance in relating symptoms to roentgenologic findings. The nerve roots leave the spinal canal laterad through the intervertebral foramina, which are located immediately behind the intervertebral disks at the interspaces. The roots of the cervical nerves emerge at the interspace *above* the vertebra of the same number. For example, the root of cervical-nerve 6 emerges at the interspace immediately above the sixth cervical vertebra, between the fifth and sixth cervical vertebrae. The root of cervical-nerve 1 emerges between the skull and the first cervical vertebra. The root of cervical-nerve 8 exits above the first thoracic vertebra, between the seventh cervical and first thoracic vertebrae.

The thoracic, lumbar, and sacral nerve roots emerge *below* the vertebral body of the same number. For example, the root of lumbar-nerve 4 emerges at the interspace below the fourth lumbar vertebra, between the fourth and fifth lumbar vertebrae. Anomalies in the number of vertebrae in any major division of the vertebral column may cause difficulty in ascertaining which root is making its exit through a particular interspace. If, for example, 4 or 6 lumbar vertebrae are present instead of the standard 5, it is not always possible to be certain clinically which nerve root is making its exit through the lumbosacral interspace. Roentgenography of the entire vertebral column and a count of the number of vertebrae from above downward probably gives the most accurate information.

DIAGNOSIS

An exhaustive description of the various conditions producing radicular pain is not practical. Similarly, it is not practical to delve into the differential diagnosis of the various conditions that produce such pain or that produce symptoms which may be confused with such pain. However, an enumeration of some of the more frequent causes of compression or inflammation of nerve roots appears appropriate.

Of the lesions causing compression of nerve roots, the most common is protrusion of an intervertebral disk. These occur in the lumbar and cervical regions most frequently, with the thoracic region a poor third. Other lesions producing radicular pain by narrowing the intervertebral foramina include hypertrophic spurs, dumbbell neurofibromas, hypertrophy of the ligamenta flava, spasm of the paravertebral musculature, and vascular malformations. Vertebral lesions that are visible roentgenologically include such conditions as tumors of the vertebral bodies, either primary or metastatic, tumors of the pedicles, such anomalies as spondylolisthesis, hypertrophic ridges at the intervertebral spaces, and traumatic lesions. Intraspinal lesions producing compression of nerve roots include gliomas, meningiomas, neurofibromas, metastatic tumors, and centrally protruded intervertebral disks. It should be noted that the majority of lesions producing compression of nerve roots are benign and are amenable to treatment.

Inflammatory lesions implicating nerve roots may act as actual masses that compress the root. Included in this category are epidural abscesses, brucellosis or pyogenic infections of the intervertebral disk, and tuberculous spondylitis. Rheumatoid spondylitis also may cause radicular pain. Tabes dorsalis, pachymeningitis, and adhesive arachnoiditis produce root pain but generally affect multiple roots. Sarcoidosis, when it affects the nervous system, may cause radicular pain. Radiculitis occurs in the course of systemic infectious diseases, in herpes zoster and other viral diseases, and in the Guillain-Barré syndrome. Finally, radiculitis of unknown origin forms a clinical syndrome of pain and paresthesia of the root type sometimes associated with weakness and changes in reflexes. The course is acute or subacute, the disorder is self-limiting and recovery is usual.

COMMENT

The differential diagnosis of the radicular syndrome must take into account two major considerations. The first is the differentiation of radicular pain from pain of other origin. Lesions of nerves, especially in the brachial or lumbosacral plexus, may cause difficulties in differentiation. The pain of periarthritis of the shoulder, coronary occlusion, osteoid osteoma, or disease of the hip joint may have a distribution resembling that of nerve-root pain. Duodenal ulcer and pancreatic carcinoma tend to awaken a patient at night. As indicated previously, pleuritic pain is aggravated by coughing and sneezing. All of these possible confusing factors must be considered in attempting to establish the presence of root pain. Secondly, as already noted, there are many causes of root pain, such as trauma, neoplasms, infections, and systemic disease. The cause is readily apparent in some instances, whereas at other times complete clinical and laboratory examination fails to uncover the cause. Special pro-

cedures involving spinal puncture and myelography are necessary at times. Even surgical exploration, when indicated, does not always give the final answer concerning the cause of radicular pain.

Guillain-Barré syndrome. The Guillain-Barré syndrome is a special form of radiculitis commonly seen in a neurologic practice. The nerve roots are considered to be the primary site of the lesions. Associated involvement of the peripheral nerves often is present and, at times, of the spinal cord, brain stem, and cerebrum. The cause is not known but has been considered in the past to be of viral origin. More recently, the concept has developed that the syndrome may be a sensitivity response of the neurons to a variety of conditions, including such entities as respiratory infections, pregnancy, malaria, and infectious mononucleosis. No precipitating cause can be found in some instances. The chief clinical signs are radicular pain, weakness of proximal as well as peripheral muscles, and reduced muscle-stretch reflexes. Muscular tenderness and atrophy frequently develop. Sense of position and vibratory sensation usually are reduced, while superficial sensation often is preserved. If superficial sensation is impaired, the distribution of the loss is usually peripheral. Facial diplegia may be present. Most commonly, all four extremities are involved symmetrically, although occasionally one extremity may be chiefly involved. Sensory loss suggesting an ascending myelitis, bulbar paralysis, and encephalitic symptoms may be present.

Findings in the cerebrospinal fluid in this syndrome are classically described as those of cell-protein dissociation. However, this dissociation is present in only 50 per cent of cases in some series. The cell count is normal or only slightly increased. The content of protein in the cerebrospinal fluid may vary from normal to 2,000 mg., with values in the neighborhood of 80 to 100 mg. occurring commonly. The prognosis for recovery with few or no residual defects is good. A definite mortality rate is associated, especially with respiratory or bulbar involvement and when patients are in the older age groups. The duration of the disability varies from three months to three years, depending on the extent of involvement and particularly on the severity of degeneration of peripheral nerves.

SUMMARY

Radicular pain possesses certain characteristics by which it can be recognized and that are valuable in the differential diagnosis of painful conditions. Radicular pain is often associated with paresthesia. Sensory diminution, muscular weakness, and diminished muscle-stretch reflexes may be present. The symptoms follow the pattern of distribution of the nerve root. The pain is aggravated by coughing, sneezing, or straining and may awaken the patient at night. Maneuvers that narrow the intervertebral foramina or that place traction on the nerve roots initiate or intensify radicular pain. Most lesions producing radicular pain do so by either compressing a nerve root or implicating the root in an inflammatory process. The primary pathologic process in many instances is benign and responds to appropriate treatment. The Guillain-Barré syndrome is a special form of polyradiculitis.

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Recent Progress in the Conquest of Pain*

JOHN S. LUNDY, M.D.
Rochester, Minnesota

I shall be arbitrary in defining "recent" as the "last twenty-five years." I suppose that it is not too controversial to trace progress for twenty-five years when recent progress is considered.

HIGHLIGHTS IN ANESTHESIA

In 1929, Zerfas reported on the intravenous use of Sodium Amytal as an anesthetic agent. In 1930, Gwathmey reported on 20,000 obstetric cases in which ether and olive oil were given by rectum as the anesthetic agent. In 1930, Leake suggested the use of vinyl ether. In 1932, Weese introduced hexobarbital sodium (Evipan) as an anesthetic for intravenous use. In the same year, Heidbrink and I developed the kinetometer gas machine with a carbon dioxide absorber. In 1933, Waters used cyclopropane clinically for the first time and that same year Goldschmidt recommended the use of divinyl ether. In 1934, I introduced thiopental sodium (Pentothal Sodium) for intravenous use. Barach reported on the use of helium in anesthesia in 1936. In 1940, Lemmon introduced continuous spinal anesthesia and Krantz and associates suggested cyprome ether.[1]

Griffith in 1942 reported on curare as a muscle relaxant. Gallamine triethyliodide (Flaxedil) is one of the series of synthetic substitutes for curare first reported on extensively by Bovet and associates in 1946. Their work in this field started with the synthesis of structures related to, but less complicated than, *d*-tubocurarine. Huguenard introduced it into treatment as the first synthetic substitute for curare in 1948. In 1949, the curariform action of the compound succinylcholine was described independently by workers in Italy, Great Britain, and the United States, and its extensive clinical trial soon followed. Edrophonium (Tensilon) was discovered as a curare antagonist as the result of a systematic analysis of the pharmacologic actions of quaternary ammonium compounds structurally related to acetylcholine and neostigmine. Although it has been studied somewhat less extensively than its congeners, Tensilon was introduced as a therapeutic agent because of its action on the skeletal neuromyal junction.[2] A number of reports on Tensilon appeared in the literature in 1950. I administered Dolitrone (5-ethyl-6-phenyl-meta-thiazane-2,4-dione) for the first time to a person on July 30, 1953, and Murphy reported on Viadryl or P55 in June 1955.

This is a brief résumé of the highlights of progress in anesthesia and analgesia. I shall discuss some of these drugs further and consider their implications for the relief of pain.

LOCAL ANESTHETIC AGENTS IN CONQUEST OF PAIN

In general, progress was greater in the last twenty-five years than in the first seventy-five years of the era of anesthesia which started in 1846. A great number of anesthetic agents for local or topical use were developed during the last twenty-five years, but they were only moderately better than the local anesthetics which had been available for fifty or sixty years, and for that reason I have omitted discussion of them. They have, however, served a good purpose in these last twenty-five years in aiding the attack on problems of pain that did not need surgical treatment.

For example, pathways of pain may be blocked by a local anesthetic agent alone or mixed with other agents which will prolong its effect for the purpose of identifying pain pathways. Many times this requires an x-ray picture to show where the points of the needles are in order to convince perhaps a neurosurgeon that the nerves should be sectioned or, in some instances, that the nerves should be destroyed chemically. Two conditions in which the latter procedure is used come to mind. The first is for patients with vascular disease of a lower extremity. In order to increase the circulation as well as reduce sensations of pain or discomfort, the sympathetic

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nerves may be destroyed with alcohol or with phenol. The results of the block may be checked by a sweating test. I think that such a procedure has a considerable future. In the arm-hand syndrome, the whole arm becomes swollen and almost useless and painful, usually because of an injury to a hand. Temporary destruction of the sympathetic nerves with alcohol in the lower part of the region gives many months of comfort and the opportunity for the physiotherapist to restore the use of the arm.

When the pathways of pain need to be identified without use of anything as drastic as alcohol or phenol, I have used a preparation of procaine, ammonium sulfate, and benzyl alcohol. With this mixture I can block the paths of pain, as a rule, for at least a day or two and sometimes longer. This is important because a local anesthetic alone does not give relief for much more than two hours.

PROGRESS IN INTRAVENOUS ANESTHESIA

The introduction of Amytal gave us an anesthetic agent that could be used by a relatively new method; that is, it could be given intravenously. This caused a great stir in medical circles, but more particularly among chemists who worked in commercial pharmaceutical houses and in the laboratories of universities. It was not long until an isomer of Amytal was produced, and one which I called "nembutal" was a considerable improvement over Amytal. The word, "nembutal," I developed by taking the "n" from the "Na" of sodium, the "e" from the ethyl radical, the "m" from the methyl radical, and the "but" from the butyl radical; the "al" is a compulsory ending for all names of barbiturates. I developed the word thus, so that if one could remember the word, he could give the chemical structure. The accepted term is now "pentobarbital."

About a year later, in 1932, as said before, Evipan, now called "Evipal" or "hexobarbital," was introduced. It was not accepted as rapidly as would be expected. Whereas the action of Amytal was too long and that of Nembutal, although shorter, was still too long, the action of Evipal was very short. However, some of the anesthesiologists had become rather discouraged about the barbiturates. Nevertheless, I was persuaded to try Evipal about 1933 and was impressed with the brevity of its action. I then became interested in the barbiturates all over again. At the same time the chemists had prepared a sulfur preparation of the barbiturate, Nembutal. This drug is known as "thiopental sodium (Pentothal Sodium)" and I used it initially on June 18, 1934. Naturally, no method of administering a drug, except by mouth, is as easy as injecting a vein. Thiopental when preceded by premedication and used in combination with nitrous oxide and oxygen also has attained high favor indeed. A reason for its popularity is that no danger of fire or explosion is associated with it.

With the advent of curare, with which relaxation could be produced well, and particularly after Tensilon was developed, which would neutralize an overdose of curare, thiopental really came into its own. As previously used with nitrous oxide and oxygen, it had not been capable of producing the required relaxation. However, introduction of a breathing tube through the larynx into the trachea, a method of controlling the atmosphere in the lungs during anesthesia, had been widely used in this country since 1930. A problem arose when thiopental was used for anesthesia during insertion of the tube because of spasm of the larynx. Soon, however, succinylcholine was made available and with it spasm of the larynx did not occur. It now seemed that success had arrived. Other relaxants were suggested and tried, but by-and-large those who used curare and those who used succinylcholine were in the majority.

This marks much of the progress that had occurred with the intravenous method until 1953.

RECTAL ANESTHESIA

The rectal method of anesthesia apparently was unattractive to most people and not much has been done with it, although tribromoethanol (Avertin), which was introduced in 1926, is still used and Pentothal Sodium also is used. It probably is particularly valuable for children when given in small doses so that they have no memory of either the anesthesia or operation.

INHALATION ANESTHESIA

The introduction of cyclopropane together with the remodeling of gas machines served an extremely useful purpose, since cyclopropane could produce relaxation. However, the fire-explosion hazard limited its favor. Divinyl ether again was not too widely accepted because it also was inflammable and was not recommended for long operations. Helium, which had proved of value in nonsurgical patients with asthma, was tried in connection with anesthetics but its favor was brief. The continuous method of spinal anesthesia, when small doses were injected at intervals, although a good method, was not widely

used because the intravenous method was so well liked. Cyprome ether and other ethers, which differed slightly from the standard diethyl ether, also were introduced at a time when these agents had to compete with the intravenous method and, therefore, did not survive in the field of anesthesia.

Against this background of progress, it is realized that further progress along identical lines may not be readily productive of agents and methods that are particularly better than those already mentioned. Therefore, it was with much satisfaction that I had an opportunity to acquire a new viewpoint concerning possible progress.

USE OF DOLITRONE FOR ANALGESIA

After I administered Dolitrone to a person for the first time on July 30, 1953, I found on pricking the skin of his forearm with a needle that he did not move his arm, although he was conscious. When the effect of the drug wore off, which it did promptly, he had no memory of the pricking. No operation was performed.

I then raised the question to myself, "Is it possible that this drug is an analgesic as well as an anesthetic?" When anesthesia of the whole person is produced, there is, of course, entire loss of consciousness as well as loss of sensation of pain; and an overdose is approached when the dose is large enough to produce anesthesia. For this reason, the anesthetist must have much training and skill in order to anesthetize patients safely. General analgesia, on the other hand, is simply the absence of pain sensation with loss of memory, but the dose of a drug to affect analgesia is much smaller and, therefore, much safer than an anesthetic dose of a drug.

It seemed to me that the quickest way to find out whether I had an analgesic was to apply it for the extraction of teeth, since the fifth cranial nerve takes care of pain sensation in the face, which includes skin, tongue and, of course, teeth. On the same day, July 30, 1953, that I first gave Dolitrone, I administered analgesic doses of the drug to 2 patients and was able to demonstrate that patients could open or close their eyes on command and also swallow on command, and that they had little memory of the extraction. This threw my readily aroused imagination into "high gear" and, while I knew I had an anesthetic agent, I was especially concerned about my hope of an era of analgesia. The investigation of this drug will be discussed more extensively in this report than some of the other agents I have investigated in the past because, in general, I applied to this drug the questions that I had applied to others in the past.

Naturally, my associates and I were concerned with any alteration that might occur in an individual while Dolitrone was being given. Pulse and respiration were counted on all occasions; blood pressure was recorded; and nothing remarkable occurred. As long as Dolitrone was used for analgesia, the electroencephalogram was found to resemble that obtained with thiopental sodium. It changes, when the Dolitrone has caused general anesthesia, to appear somewhat like that obtained when cyclopropane has caused general anesthesia.[3] The most reliable test of the condition of the heart which can be used for our purposes is an electrocardiogram and we saw nothing alarming in it. Finally, after the drug had been administered almost three hundred times, one of the men noticed that while an electrocardiogram was being made, the blood pressure had fallen markedly and an extraventricular beat of the heart occurred. This alarmed him because the ventricles, particularly the left ventricle, is the portion of the heart which pumps the blood to the body, and if it should become irregular enough, the patient would die. Because of this observation, electrocardiograms were made on a number of patients while they were receiving the drug. It seems to me that the last preparation of the agent which we have been using does not cause this phenomenon. I am not sure about the first preparations.

Preparations. The first preparation of Dolitrone that I received was in crystals and was then dissolved in a 1:1,500 solution of sodium hydroxide; the resulting 2.5 per cent solution had a pH of 11.4. This was much too alkaline, and I expected and saw a few cases of thrombophlebitis after its administration.

The next preparation was a suspension of the drug in 50 per cent polyethylene glycol 200. The suspension of Dolitrone in this glycerin-like material was hoped to make the drug go into solution more easily. The crystals had been difficult to dissolve and came out of solution in about one and one-half hours. When the material in this suspension was put into solution with the same sodium hydroxide solution, the pH of the 2.5 per cent solution remained 11.4. The drug, however, went into solution much more easily than the crystalline form and stayed there longer.

During the latter part of 1954 and thus far in 1955, I have been receiving a certain amount of Dolitrone that has been lyophilized. This simply means that all the water has been extract-

ed from the drug, leaving it fluffy and easily dissolved in sterile water; 10.4 is the pH of a 2.5 per cent solution, the same as of a 2.5 per cent solution of thiopental sodium which has been used innumerable times. The reduction in alkalinity from a pH of 11.4 to 10.4 is in the nature of 10 times, or more than anyone except a chemist might suspect. The problem now is to manufacture this material in quantity and to keep the quality up to standard. Then an extensive trial of the agent can be made.

Various effects. Certain interesting effects have been noted. For example, after consultation with Dr. J. L. Bollman, I was encouraged to give the suspension of Dolitrone intravenously without putting it into solution. Good effects were achieved when given in this manner, although my experience with such administration is limited. I did, however, inject 1 gm. of the Dolitrone suspension (10 cc.) intramuscularly into the buttocks of a patient who was dying from cancer and was in great pain. She complained of a stinging sensation for two minutes after the injection; whether the pH of the suspension, which is 6.6, was responsible, I am not sure. However, in another three minutes her pain was gone and she had almost two hours of relief.

I had a similar experience with a young man who had a traumatic wry neck. He was unable to stoop over, tee up a golf ball, turn his neck, or swing his golf clubs. He also experienced a stinging sensation for two minutes after intramuscular injection of the suspension of Dolitrone. In another three minutes his pain was gone and relief lasted about two hours, during which time he could make various movements. In each case, no other drug effect could be seen except that they said their pain was relieved.

These two experiences have led me to hope that since no other sign of drug effect was noted with the intramuscular administration of this drug, perhaps it should be tried in obstetrics.

Not much of the investigation of an analgesic can be done in the animal laboratory. Toxicity can be studied there, and also whether or not large doses produce anesthesia can be determined. To find out about the analgesic effect, however, the subject must be able to talk. This means, perhaps, that the chemists will need to re-investigate the analgesic effects of drugs which they had hoped would be anesthetic agents and have discarded because the animal could not be anesthetized with them.

Less bleeding with Dolitrone than with thiopental sodium was observed by one of the dental surgeons, and parenthetically I may say that Seldon pointed out in his thesis that nitrous oxide is about the only general anesthetic agent which does not dilate the capillaries. On introduction of ethylene, cyclopropane, ether, and thiopental, the surgeons complained about the oozing of blood in the wound. Seldon[4] gave a dose of Dolitrone to a rabbit which had a Clark window in its ear for studying the capillaries. He found that Dolitrone did not dilate the capillaries. This discovery led to my making some further observations on the effects of nitrous oxide and Dolitrone. I found that the skin temperature of a patient rose when preliminary medication was given, and that the skin temperature was a true test for dilatation of blood vessels. I had hoped that with Dolitrone and nitrous oxide I would be able to determine the skin temperatures during either surgical sympathectomy or chemical sympathectomy and know by a pronounced increase in the temperature of the extremities before the wound was closed that the operation was successful. This, I realize, would not work well if pronounced disease of the blood vessels were present, but I thought it was worth while to consider.

In Terpinas' thesis[5] the oxygen saturation of arterial blood during anesthesia with thiopental, nitrous oxide, and oxygen is compared with the saturation when Dolitrone was substituted for thiopental to produce the anesthesia. Data were gathered concerning 25 patients who received Dolitrone, and the data on arterial oxygen saturation showed that if more nitrous oxide and less oxygen were administered, less Dolitrone was needed than when a small quantity of nitrous oxide and oxygen was used. Comparison of the thiopental series and the Dolitrone series showed clearly that most of those who received Dolitrone had a higher oxygen saturation of arterial blood than those who received thiopental.

This, I thought, perhaps was due to the fact that respirations were deeper with Dolitrone than with thiopental. However, in both series patients received adequate amounts of oxygen.

When thiopental is used alone, a breathing tube is difficult to place through the larynx and into the trachea because of spasm of the larynx. This, of course, is extremely important in operations within the chest, such as on the lungs and on the heart. I observed that with Dolitrone little or no spasm of the larynx developed, and I thought of the bronchoscopist who must introduce his lighted instrument through the larynx and into the trachea so that he can observe and

work on the respiratory passages. All of this, of course, would have been of extreme importance some time ago before the introduction of succinylcholine, a muscle relaxant. However, when succinylcholine is given intravenously, the larynx does not go into spasm and intubation is easy. This is fortunate for us so that we may use it with thiopental. However, if succinylcholine is administered and the patient does not breathe well thereafter, there is no antidote for it. For curare we have an antidote in Tensilon. The combination of thiopental and curare, however, does not prevent laryngospasm, whereas Dolitrone and curare may be combined without laryngospasm. Thus, one is encouraged to consider Dolitrone for operations on the larynx.

Chemical structure. The chemical structure of Dolitrone is shown in figure 1. The chemical formula is 5-ethyl-6-phenyl-meta-thiazane-2, 4-dione, wherein meta-thiazane signifies a 6-membered heterocyclic ring containing 1 atom each of sulfur and nitrogen and 4 carbon atoms, the sulfur and nitrogen atoms being in the meta or 1,3 positions relative to each other. The ending "ane" signifies a saturated ring. In the structural formula the sulfur atom is in position 1. The ethyl group is in position 5, the phenyl group in position 6, and the keto (=0) groups are in positions 2 and 4, as is indicated by the 2, 4-dione element of the name.

For me to enter the field of chemistry may be presumptuous. Nevertheless, the fact that I can read a structural formula and have administered sedative, analgesic, and anesthetic agents to thousands of people once led me to conjecture, from the structural formula of a newly introduced product, that it would be a "short-acting" substance. Later this proved to be true. In the structural formula of Dolitrone, I noticed that 2 double-bonded oxygen atoms are linked, each to a carbon atom that is part of the central heterocyclic ring, and the nearer such double-bonded oxygens are to the nucleus of a compound the better, it seems, are its local analgesic properties. At any rate, Dr. F. T. Maher, pharmacologist at the Mayo Clinic and Foundation, has

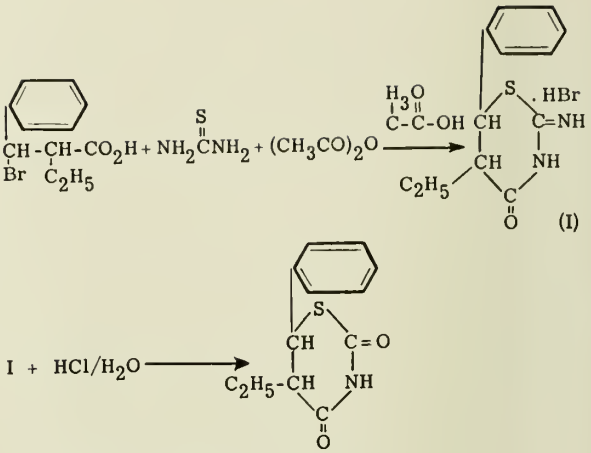

Fig. 1. Structural formula for Dolitrone.

produced corneal analgesia by topical application of a 10 per cent suspension of Dolitrone in polyethylene glycol to the eye of a rabbit.[3]

COMMENT

Time will not permit complete enumeration of all observations that have been made, but I feel sure that those presented illustrate recent progress in the conquest of pain. Certain needs have not yet been met. If the intramuscular administration of Dolitrone in suspension would facilitate care of the walking wounded, it would become important in the measures which are presently employed in war and in disaster. The conquest of pain is not limited actually to surgical operations. There is, I hope, a field in obstetrics where this drug may become useful. At a recent tonsillectomy I was able to produce both amnesia and analgesia with Dolitrone.

At the moment I am arranging for the investigation of a new intravenous anesthetic called "Viadryl" or "P55." It is a steroid, and as far as I know, the first steroid to be suggested as an anesthetic agent. Viadryl or P55 in contrast to Dolitrone is advocated for long operations lasting from one and one-half to nine hours. It will be interesting to see where viadryl or P55 fits into our future needs for the relief of surgical pain. I am grateful that I do not as yet see the end of progress in the conquest of pain.

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Successful Chemical Sympathectomy for Left-Sided Shoulder Pain After a Cerebrovascular Accident

Report of a Case

JOHN S. LUNDY, M.D.
Rochester, Minnesota

In every branch of medicine occasions arise when the technic of a procedure is far more complex and critical than the action which the procedure is designed to carry out. This is particularly true of certain applications of chemical sympathectomy for the relief of pain. The action produced by this procedure is relatively simple and is readily understood. Success of the procedure, however, is another thing. It is not a matter of routine practice. Rather, it depends almost wholly on the precision with which the points of the needles are placed and restriction of the quantity of alcohol injected to 0.5 cc. at a time. The exercise of extreme care in these respects will ensure that the desired spot is wetted, so to speak, with each small injection. This in turn means that the tendency for the solution to spread will be less than would be the case if all of it were injected at one time in continuous injection.

The following case demonstrates the paramount importance of technic in successful alleviation of persistent pain by chemical sympathectomy.

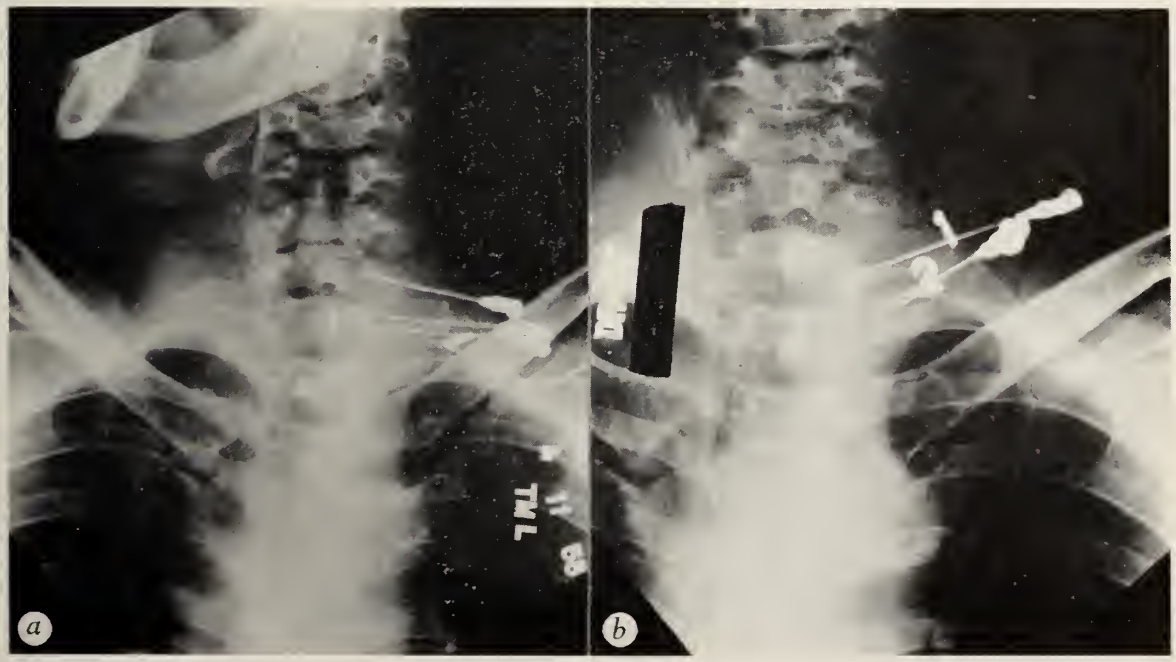

Fig. 1*a*. In chemical sympathectomy done on April 11, 1955, points of the needles were medial to the shadows of the pedicles, and the block failed; (*b*) in chemical sympathectomy done on April 18, 1955, needles were situated lateral to the shadows of the pedicles, and same quantity of alcohol as injected on April 11 gave the desired result.

REPORT OF CASE

A 46-year-old man sustained a cerebrovascular accident on June 13, 1953. About six months later he began to experience left-sided pain in the shoulder. This pain spread to the arm and hand. On March 12, 1954, hydrocortisone was injected into the left shoulder joint, and this afforded the patient considerable relief from pain. Very nearly full motion returned. He noticed some difficulty down the left side of his throat when he swallowed, and weakness of the left arm and some degree of weakness of the left leg. He had undergone a number of operations over the years prior to his stroke; these, however, were not related to the effort to treat his shoulder-hand syndrome. His pain had become severe, and he no longer benefited by physical therapy.

At consultation I recommended that left stellate ganglion block be carried out with alcohol. This was accepted. Needles were placed and on April 11, 1955, a roentgenogram was made as shown in figure 1*a*. He complained considerably of pain when the needles were placed, and, for that reason, 8 cc. of a 2.5 per cent solution of Pentothal Sodium was injected intravenously. Using the spot-wetting technic, I injected 0.5 cc. of alcohol at a time until a total of 3 cc. of absolute alcohol had been deposited in the area of the left side of the first thoracic vertebra. I was uncertain that any increase in temperature of the left hand had been obtained after the block. Horner's syndrome was absent.

On the next day, 37.5 mg. of hydrocortisone was injected into the left shoulder joint because the patient had obtained no relief of pain from the block performed on April 11. However, a sweating test carried out on April 13 showed that no effect had resulted from the stellate ganglion block attempted April 11 (figure 2).

A week later the block was repeated, and the needles were placed as shown in figure 1*b*. The patient again received Pentothal Sodium intravenously. Using the spot-wetting technic, I injected 2.5 cc. of absolute alcohol through each of two needles, one in the area of the left side of the first thoracic vertebra and one in the same area of the second thoracic vertebra. Immediately after the injection, the patient's left hand obviously was much warmer, and a mild version of Horner's syndrome appeared on the left. He also seemed to have less pain. A sweating test done on April 19 showed that the block had been entirely satisfactory, as represented in figure 2.

This patient estimated that he had obtained at least 75 per cent relief because of chemical sympathectomy.

On April 21, he told his physician that pain in the shoulder and hand had been reduced by about two thirds, and that the range of motion at the shoulder was almost complete. Movements of the left fingers were much less painful, with the result that physical medicine was to be continued. It should be successful.

COMMENT

This case illustrates rather strikingly both the correct and the incorrect way to carry out stellate ganglion or cervical sympathetic block with alcohol. An impression of the precision with which needles must be placed can be gained from the roentgenograms; that is, the point of the needle must be lateral to the shadow of the pedicle of the vertebra. If it is not, the small quantity of alcohol that can be used will not be sufficient to cover the sympathetic nerves.

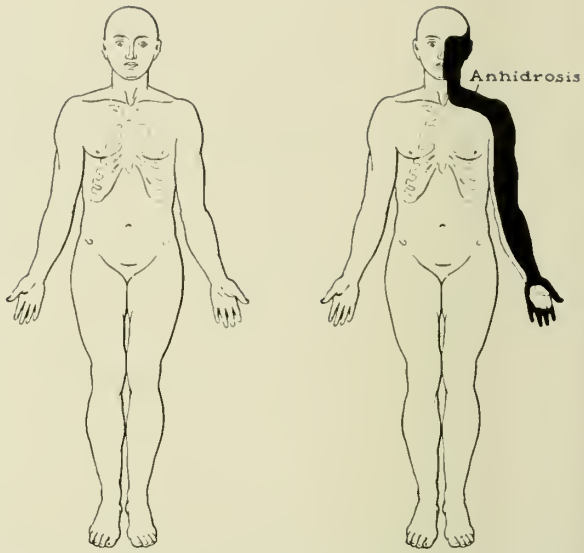

Fig. 2. (*Left*) Sweating test after block done on April 11; (*right*) sweating test done after block performed on April 18, 1955.

The foregoing considerations indicate the outstanding factor inherent in performance of therapeutic block with alcohol or 6 per cent solution of phenol in water, which is that if the needle is precisely placed, the quantity of solution used can be so small that untoward results will not occur. That is, the amount of alcohol that is injected will not spread and come into contact with tissue that could be damaged by the alcohol.

A minor point may be mentioned here in respect to the block for surgical anesthesia in which a solution of local anesthetic agent is used. In such an instance, if the needle is in any proximity to the nerve trunk, the whole area can be flooded and the desired result can be obtained, so far as anesthesia is concerned. Untoward results of such wide dispersal of the agent can be avoided by the use of a mixture of 1 per cent solution of procaine hydrochloride, a 2.5 per cent solution of ammonium sulfate and a 2 per cent solution of benzyl alcohol. With such a mixture considerable increase will be effected in the duration of relief of pain over that which follows the use of a local anesthetic agent alone, yet flooding of the area with the mixture will not produce untoward results.[1]

Chemical lumbar sympathectomy and chemical cervical sympathectomy, in my experience, have proved to be helpful when pain in the extremity, with poor circulation, requires attention.

REFERENCE

1. Lundy, J. S.: Diagnostic and therapeutic nerve blocks: their use in combating "pathologic" pain. Arizona Med. 10:283-285, 1953.

Editorial

PAIN, THE MANY-VISAGED ENIGMA

THE ENIGMA of pain provokes the attention of the investigator because thus far it has remained an enigma with as many varieties as there are shades of color in the visible spectrum. Hence, at present it is not always possible to find the cause for a given pain. Incessant industry in research no doubt will result in the eventual demonstration of the cause for most pains. Until that bright day of the future, however, we shall have to rely on those methods of relief which are available to us, without knowing the genesis of the distress. This of course is only half an answer to the problem, but it will probably capture the applause of the patient.

A good grasp of the problem of root pain is not easy to come by within the short space of a paper in a journal, but in the paper, "Radicular Pain (Including the Guillain-Barré Syndrome)," the author manages to contribute to that result.

An often vexatious and at times frustrating problem is brought out and examined in some detail in the report, "Successful Chemical Sympathectomy for Left-Sided Shoulder Pain After a Cerebrovascular Accident." The report demonstrates how a relatively simple therapeutic procedure, strikingly effective when correctly performed, can be entirely vitiated if meticulous attention is not given to technic when the procedure is employed.

In another piece, "Recent Progress in the Conquest of Pain," the experience of twenty-five years in dealing with surgical pain is reflected, but there is actually more to it than that. The vista of a new era of analgesia that is different from analgesia as commonly understood is briefly sketched, and a thoroughly modern approach to the problem of therapeutic nerve block emerges from a quarter century of experience, which includes all the agents and procedures in use today as well as those that have fallen into unremembered desuetude.

JOHN S. LUNDY, M.D.

Book Reviews on Pain

GERIATRIC ANESTHESIA, by PAUL H. LORHAN, M.D., professor of anesthesiology, department of anesthesiology, University of Kansas Medical Center, Kansas City, Kansas, 1955. Springfield, Illinois: Charles C Thomas, 90 pages. $3.25.

The list of 39 references to articles dealing with geriatric anesthesia or some phase of it is evidence, if the list is complete, of the dearth of material on this subject, and the reader can easily understand why the author has written the book. He covers his subject of geriatric anesthesia by commenting on the following points: general consideration, physiologic changes in the aged, preoperative preparation, surgical management, preanesthetic medication, choice of an anesthetic, anesthetic management, postoperative management, and summary. These phases of his comments are included in a table of contents, but, unfortunately, an index is not included. Early in the book, the author indicates that he considers "agedness" on a biological basis and not just in terms of years that have been lived.

Although many conditions are considered briefly, the points which the author considers vital have been emphasized under such subjects as physiologic changes, external changes, changes in bone, cardiovascular changes, respiratory changes, emphysema, pulmonary fibrosis, gastrointestinal changes, genitourinary changes, and changes in the nervous system and the blood. Condensed statements are made relative to preoperative preparation, fluid and electrolyte balance, blood volume anemia and diabetes, as well as the various vitamins, that is, vitamins A, B, C, D, and K. He mentions heart disease, which drugs may be used for this condition, and the dose that may be used for digitalization. Pulmonary embolism also is covered briefly. The author gives consideration to the use of cortisone and ACTH and to the advance prophylactic preparation of the patient in order to avoid shock. Remarks on surgical management are brief; more time is spent on preanesthetic medication.

Various anesthetic agents are discussed and essential points pertaining to each are made; local infiltration and regional and spinal anesthesia are considered as well as the muscle relaxants. The author stresses that "in administering anesthesia to the aged, the skill and judgment of the anesthesiologist are of the greatest importance." He points out the additional severe risk of an emergency operation on a geriatric patient as compared to the risk of an elective operation.

Various aids that may be used to support the patient during the postoperative period are discussed.

The book is easy to read, is printed on good paper, and is attractive in size with a flexible cover. It represents again the need that is met when an author confines his attention to a specific subject. Anyone who feels that geriatric anesthesia is not a special problem would do well to familiarize himself with this book so that he may know the current status of geriatric anesthesia.

JOHN S. LUNDY, M.D.

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A MANUAL ON CARDIAC RESUSCITATION, by ROBERT M. HOSLER, M.D., 1954. Springfield, Illinois: Charles C Thomas, 183 pages. Price $4.00.

In this small book is gathered the most pertinent knowledge concerning cardiac resuscitation, especially during anesthesia and operation. It has been carefully prepared and indexed and a bibliography has been included. The number of illustrations are sufficient. Those who work in the operating room will find the book helpful in such emergencies as cardiac arrest.

JOHN S. LUNDY, M.D.

Section on PAIN

Current Literature on Pain

USE OF ORAL PROCAINE IN CONTROL OF PRURITUS, by Beinhauer, L. G. Arch. Dermat. & Syph. 69:188-194, 1954.

"The following report covers the results of the treatment of pruritus with procaine hydrochloride administered orally. One hundred forty-five patients, representing 23 pruritic dermatoses, were studied. Seventy-eight patients had received no previous medication, and the remaining 67 had received no relief from varied types of therapy previously administered. In the later group were included 20 patients previously treated with intravenous injections of procaine, without relief. . . . . Reactions occurred in 12 patients (8.2 per cent) and were minor, consisting of headache, dizziness, nausea, drowsiness, and vomiting. These were readily controlled by withdrawal of the drug and did not recur upon readministration. In patients in whom response was favorable, relief was forthcoming within four days after treatment was begun. No evidence of adverse systemic effects was noted when the drug was given over long periods of time. Oral procaine therapy was found to give complete relief in 22.2 per cent of the patients, temporary relief in 27.9 per cent, and failure in 49.9 per cent. Oral procaine hydrochloride-ascorbic acid medication gave most effective response in the treatment of urticaria (penicillin), herpes zoster, and burning tongue. Generally speaking, the effectiveness of orally administered procaine for the control of pruritus did not exceed that of other recognized therapies prescribd for the same purpose in similar dermatoses. Procaine can be administered orally with safety and warrants a trial when other therapy fails. Our results did not rate in merit with the enthusiastic results previously reported by others."

From Lundy, J. S., and McQuillen, Florence A.: Anesthesia Abstracts. Minneapolis: Burgess Publishing Company, 1954, Vol. 40. Copyright by J. S. Lundy.

HYPERNEA HYPOREACTIVITY AND THE ILL-MET TRIAD: NEWER ASPECTS OF ANESTHETIC COMPLICATIONS, DEATH BY MISADVENTURE, ANAPHYLACTOID AND DRUG REACTIONS DERIVED FROM INSPECTION OF THE RESPIRATORY PASSAGES, by Baggot, M. G. Anesth. & Analg. 33:309-317, 1954.

"The common problems which interest the anesthesiologist may be classified as follows: 1. Those related to existing diseases of the patient, such as ruptured uterus, coronary occlusion, epilepsy. 2. Those incidental to the surgical procedures, such as paralysis of the diaphragm due to acute tension pneumoperitoneum and mediastinal emphysema. 3. Those which are common to apparently healthy individuals with trivial local lesions, who have been exposed only to the techniques and drugs of anesthesia. For purposes of discussion this last group can be considered true anesthetic complications, and forms the basis of this paper. . . . . Why anesthetic complications should occur, characteristically, while the patient is in the process of induction or recovery, has yet to be explained. That is whenever, though the higher centers are obtunded, the reflex sensibilities are active. In this connection attention should be directed to the hypernea which is the cardinal feature in the stage of excitement. The more rapid the induction, the more intense the hypernea. . . . .

"Experienced anesthetists have learned that a slow induction, with whatever agent, is safest. . . . . The general failure to appreciate the dangers of the exaggerated hypernea produced by precipitate induction is reflected in the high incidence of complications associated with the misuse of pentothal curare mixtures. . . . . Throughout the respiratory tract there are a number of trigger zones, mechanical stimulation of which will produce a variety of phenomena. . . . . Recognition of this ill-met triad composed of a (a) hypernea (b) missile, (accumulated mucus or gastric fluid) free within the air passages and (c) trigger zones present throughout the respiratory system, clarifies the mechanism of several disorders and the control thereof. While these three factors individually are commonplace, their coincidence and its importance with and without reference to anesthesia have been neglected. . . . . To reduce the incidence of complications, major and minor, during anesthesia, the following measures are recommended: 1. The stomach and esophagus first of all should be cleared of material other than minimal air. This can be done simply by adapting the technique of endotracheal toilet. . . . . The Levine tube is ideal for this purpose. . . . . 2. The patient directly before administration should be made to cough, clear his throat, and blow his nose. . . . . 3. Most illuminating is preliminary inspection with a laryngoscope of the upper air passages. . . . . Though anesthesia is necessary thoroughly to clear the respiratory tract, topical agents must not be used. The introduction of liquid into the airway violates the first rule of anesthesia (keep the airway clear). . . . . Induction of anesthesia must be achieved without the production of hypernea. For this purpose a dilute solution of an intravenous barbiturate is most easily controlled. . . . .

"Because of failure to recognize reflex apnea, it has been the general belief that the intravenous barbiturates are especially liable to cause respiratory depression. Attempting to apply this misconception I have tried deliberately to produce a transient apnea which would permit intubation before the hypernea developed. Doses up to one gram of an intravenous barbiturate were forcibly injected through a 15-gauge needle. Instead of respiratory arrest this produced a constant and extreme hypernea as the stage of excitement was concentrated into seconds. With the airway clear nothing remarkable was noted other than odiferous gas, being freely excreted from the lungs. In connection with the transient breath-holding which occurs following a small dose of an ultra short-acting barbiturate, aside from visible irritants in the respiratory tract, one must consider the vapor entering the alveoli from the bloodstream. This product of barbiturate and water may have a slightly irritating effect analogous to that of ether vapor. . . . . Before the patient develops hypernea in the recovery process, routine inspection of the airway should be repeated. At any time appearance of one or more components of the aspiration syndrome calls for immediate removal of the irritant, using adequate medication if the patient is not already in deep coma. Here the pentothal curare mixture is most valuable. . . . . Familiarity with the ill-met triad shows that the intrinsic hazards of the anesthetic drugs have been exaggerated and the complications typical of, though not peculiar to, anesthesia occur where it is incomplete and technique faulty."

From Lundy, J. S., and McQuillen, Florence A.: Anesthesia Abstracts. Minneapolis: Burgess Publishing Company, 1954, Vol. 40. Copyright by J. S. Lundy.

(Continued from page 314)

author includes a comprehensive review of the pertinent literature which is well indexed at the end of each chapter and consists of a cumulative total of over 100 pages of references. Almost all chapters have been expanded with the inclusion of more functional pathology and basic rationale of therapy, especially on pernicious anemia, the iron deficiency anemias, and iron metabolism. The sections on the classification of the anemias and the hemorrhagic states also have been expanded and greatly improved, giving the reader a more workable understanding of the inter-relationship of the various disorders. The chapters on pernicious anemia, aplastic anemias, and agranulocytosis are especially outstanding. Also included in this book are discussions on the sternal puncture, blood transfusions and blood substitutes, as well as a technic for a simple test for demonstrating the "L.E." phenomenon. Little attention is given to basic cytology and hematopoiesis, and the 9 color plates are not of good quality. The type is large and very readable. There are 78 illustrations and 79 figures. The line drawings in particular are very illustrative of the material presented.

This book is basically sound and should prove of value to the student and practitioner alike. The historic content and the documentation of the world's literature on this subject should be of great interest and use even to the specialist in hematology.

ROBERT E. RYDELL, M.D.

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Hernia: The Pathologic Anatomy and Their Anatomic Repair of the More Common Hernias, by CHESTER B. MCVAY, M.D. Edited by ALTON OCHSNER, M.D., 1954. Springfield, Illinois: Charles C Thomas. 40 pages. $4.75.

Dr. McVay presents a very readable atlas of the common types of hernia and their repair. Each hernia is accompanied by an excellent series of drawings showing first the pathologic anatomy and then one good method of surgical repair. Usefulness is enhanced by an arrangement of material which allows the text for the figures to be on the same or facing page. Short essays stressing anatomic and clinical aspects of each hernia are included. The importance of the tranversus abdominal muscle and its aponeurosis in the repair of parietal abdominal hernias is emphasized.

Sections on diaphragmatic, epigastric, umbilical, inguinal and femoral, incisional, and pelvic and lumbar hernias are included. The short transverse epigastric incision recommended for diaphragmatic hernia repair often offers insufficient surgical exposure; the midline supraumbilical sternal splitting incision could be mentioned as a procedure allowing excellent exposure for diaphragmatic hernia repair as well as for gastric surgery. The section on the repair of inguinal and femoral hernias, of which Dr. McVay is an authority, is especially praiseworthy.

The sound principles, illustrations, and concise presentation make this an excellent atlas. Every student in surgery should have access to a copy.

G. S. CAMPBELL, M.D.

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Reproducitve System, Ciba Collection of Medical Illustrations, by FRANK H. NETTER, M.D., 1954. Summit, New Jersey: Ciba Pharmaceutical Products, Inc., Volume 2. $13.00.

This beautifully prepared volume of medical illustrations represents normal and pathologic anatomy of male and female genital systems. The colored illustrations by Dr. Netter leave nothing to be desired as to clarity, particularly in his representation of the anatomy of the parts in both male and female.

The accompanying text, although briefly given, should serve as an excellent review of the diseases commonly met by both the urologist and gynecologist. It should be of great value to the general practitioner.

SAMUEL S. BEIRSTEIN, M.D.

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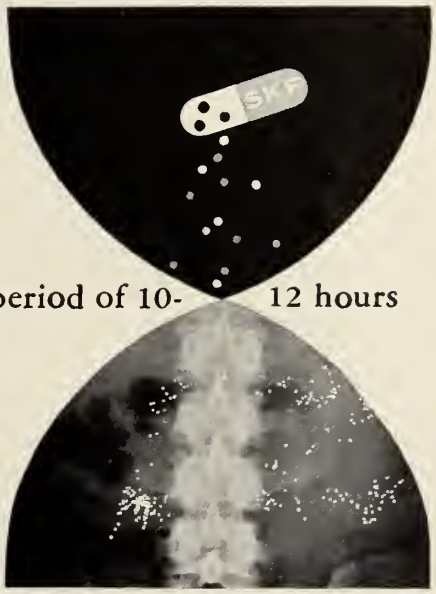

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American College Health Association News . . .

The papers and proceedings of the thirty-third annual meeting of the American College Health Association held in Colorado Springs, April 28 through 30, will be published in one volume some time late this summer. All members will receive a copy.

Officers for next year will be: president, John W. Brown, M.D., University of California, Berkeley; vice-president, Helen M. Rossiter, M.D., University of Western Ontario, London, Ontario; president-elect, Paul L. White, M.D., University of Texas, Austin; and secretary-treasurer, Irvin W. Sander, M.D., Wayne University, Detroit.

Newly elected council members for a three-year term are: Lewis Barbato, M.D., University of Denver, and Frank R. Smith, Jr., M.D., The Johns Hopkins University, Baltimore.

By action of the council the 1956 meeting will be in Minneapolis May 17 through 19. The University of Minnesota will be the host school and Dr. Ruth Boynton is the chairman of the local arrangements committee. The 1957 meeting will be in Baltimore, Maryland, with the Maryland group acting as hosts and Dr. Frank R. Smith, Jr. has been asked to be chairman of 1957 local arrangements committee. Probable dates of the 1957 meeting will be April 25 through 27.

SECTION ACTIVITIES

The following officers will serve the South Central Section of the American College Health Association for 1955-56:

President, George A. Trimble, M.D., University of Missouri; vice-president, S. I. Fuenning, M.D., University of Nebraska; and secretary-treasurer, Alta V. Bergquist, R.N., B.S., Nebraska State Teachers College, Kearney.

South Central Section is comprised of colleges and universities in Missouri, Kansas, and Nebraska. This section was co-host at the recent national meeting in Colorado Springs.

At the 1955 meeting of the Michigan Section of the American College Health Association held May 27, 1955, at the Student Union, Michigan State University, East Lansing, Michigan, the following officers were elected: president, Barbara Boger, M.S.W., Michigan State University, and secretary-treasurer, Mrs. Marian Kelly, Jackson Junior College.

The panel discussions concerned with problems of admission, certification for placement, and the emotionally maladjusted comprised the major portion of the program for the meeting.

Dr. Clifford Menzies of Michigan State University gave a resume of the national meeting in Colorado Springs. Dr. Warren Forsythe of the University of Michigan was the luncheon speaker and talked of his retirement plans after July 1, 1955.

PERSONNEL

George J. Prochow, M.D., has been appointed to the staff of the Health Service at Kent State University, Kent, Ohio as of July 1, 1955. Dr. Prochow has been a student health physician at the University of Chicago.

(Continued on page 34A)

ABORT BOILS with FOSSEL

Non-suppurating boils can often be aborted without resorting to the lance. Fossel Ointment provides three important benefits for incipient boils:

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**Diseases of the Skin,* 6th ed., 1943, p. 343.

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ACHA NEWS

(Continued from page 32A)

Montana State University, Missoula, Montana, announces the appointment of a new director of the Student Health Service Program, Harold A. Braun, M.D., of Philadelphia. Dr. Braun will take over his new duties at Montana State on July 1, 1955.

Miss Vivian Weedon, curriculum consultant for the National Safety Council announces that the report of the cooperative project of the American College Health Association and the National Safety Council is available. The title of the report is "Safety Monograph for Colleges and Universities, No. 3, Survey of Accidents to College Students." The supply is limited, but while it lasts it is available from the National Safety Council, 425 North Michigan Avenue, Chicago 11. Miss Weedon adds that requests will receive more prompt attention if her name is mentioned.

The Proceedings of the Fourth National Conference, held in New York in May, 1954, are now available and may be purchased for $2.00 per copy from the office of the secretary-treasurer, Irvin W. Sander, M.D., Student Health Service, Wayne University, 5050 Cass Avenue, Detroit 2, Michigan. A wealth of worthwhile material is included and, according to Dr. Dana L. Farnsworth who edited the Proceedings, it should be available to all student health personnel and other university or college officers concerned in any way with the health problems of students. One copy will be sent to all registrants at the Fourth National Conference.

EXPANSION PLANS

The University of Delaware has received a gift of $300,000 for a new Student Health Center. Dr. Gordon Keppel, director of student health, says that at present they are consulting with the architect over blueprints.

Evelyn Ballard, M.D., medical director at San Francisco State College, announces plans to expand Health Service facilities within the next year on completion of their new building. They are considering addition of a full-time college physician this fall.

News Briefs . . .

North Dakota

Sheyenne Memorial Hospital for the chronically ill was dedicated recently as a feature of the seventeenth annual meeting of the Lutheran Hospitals and Homes Society in Valley City. The 60-bed institution is operated by the Society. Dr. Russel Saxvik, superintendent of the State Hospital at Jamestown, traced the history of recent hospital progress in his dedicatory address and confirmed the need for a hospital such as Sheyenne Memorial.

* * * *

Dr. H. E. French, dean emeritus of the University of North Dakota School of Medicine at Grand Forks, has invited medical students to an annual dinner at his home since 1911. This year the affair turned into a reception in his honor.

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Dr. O. C. Gaebe was honored at the North Dakota State Medical Association Convention for his fifty-year membership in the North Dakota State Medical Society. Still very active, Dr. Gaebe answers emergency calls just as he did fifty years ago.

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Dr. Robert M. Fawcett, who has been associated with the Lake Region Clinic in Devils Lake since 1948, was recently elected to membership in the American College of Physicians.

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

The Nature and Treatment of Parkinsonism

SIDNEY K. SHAPIRO, M.D.

Minneapolis, Minnesota

Although the substantia nigra and corpus striatum appear to be involved more often than other areas of the brain, a careful review of the literature reveals that there is no constant pathologic substrate for parkinsonism. It is impossible to predict what the postmortem examination of a brain will reveal in any given case of parkinsonism, and, conversely, the degree or severity of the parkinsonism is not possible to determine from a pathologic examination itself, or, in fact, even whether the patient suffers from parkinsonism. Attempts have been made to classify parkinsonism in many ways and various authors have classified parkinsonism on the basis of the clinical picture. No accurate way is known of classifying parkinsonism on the basis of etiology from the clinical picture presented by the patient. The only reasonable basis for the classification of parkinsonism is on the basis of the presumptive etiologic factor. The best classification appears to be in 2 main groups: (1) a large group due to unknown causes, and (2) symptomatic parkinsonism in which the etiology of the condition is known. In this latter group fall (a) the postencephalitic, (b) vascular or arteriosclerotic, (c) manganese, carbon monoxide, and carbon disulfide toxicoses, and (d) those with tumors Parkinsonism is a syndrome and not a disease entity. From a practical standpoint, parkinsonism occurring in the older age group presents a more difficult treatment problem because of the decreased tolerance of these older patients to medication. The literature is most confusing concerning the clinical symptomatology that should be included under the term "parkinsonism." If the picture of pure extrapyramidal disease is considered, characterized by tremor and rigidity at one end of the scale and the picture of diffuse brain involvement at the other end, then it is relatively easy to realize the way in which the pure picture of extrapyramidal disease merges with that of diffuse brain involvement and how all degrees of combination of diffuse brain disease and pure extrapyramidal involvement can be encountered. From the standpoint of prognosis and response to treatment, the term parkinsonism is best limited to the clinical symptomatology described in the original monograph of parkinsonism and as previously outlined—namely, the picture of pure rigidity and tremor. It is in this group of patients, in which the intellect is uninvolved, that the best therapeutic results are encountered. In the group of patients with deterioration, who also have a parkinsonian syndrome of tremor and rigidity, the results of treatment are poor. As the patient passes from the picture of pure tremor and rigidity to the opposite end of the scale in which diffuse brain involvement is encountered, the results of therapy and the ultimate prognosis decrease proportionately.

To date no specific therapy is available which

SIDNEY K. SHAPIRO, *a 1943 graduate of the University of Western Ontario Faculty of Medicine, London, Ontario, is a specialist in neurology and psychiatry in Minneapolis.*

From the Division of Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

can remedy or halt the progressive pathologic changes in the central nervous system which are responsible for this condition. All therapies are of necessity symptomatic and directed toward the troublesome symptoms of the disease. The use of all drugs that are at present available effects a 40 to 50 per cent improvement in the patient's symptomatology under optimum conditions. It becomes evident that any treatment program which relies solely on drug therapy is doomed to failure. Careful consideration must also be given to the emotional rehabilitation of the patient so that he can continue to carry on in spite of residual symptomatology.

The emotional rehabilitation of the patient does not imply that intensive formal psychotherapy is necessary. It indicates that a practical sympathetic approach to the patient as a whole is necessary. At the time the diagnosis is established and before drug therapy is commenced, we find it advantageous to have a frank discussion with the patient about the nature of his condition. He is told that his condition is due to a disease involving the central nervous system and that to date we are unable to repair the damaged areas of the brain. He is told that his condition is benevolent, in that most patients with parkinsonism live a normal life span and that within certain limitations he can continue to carry on as formerly. In this regard, a rough analogy is made to the patient with quiescent tuberculosis. The patient with tuberculosis is, from a practical standpoint, not considered cured but if he lives within certain limitations after the subsidence of the acute phase of his disease, he can carry on normally for an indefinite period. Similarly, the patient with parkinsonism must expect to limit his activities to some extent because of the nature of the disease. The amount of exercise and activity which he can tolerate is that which falls just short of the amount which would cause fatigue. At the initial interview the patient is told that this condition will never affect his mentality and that he will not become demented or insane from parkinsonism. In addition, he is told that he will never become paralyzed and that any difficulty in motor function is due to rigidity and not paralysis. Many patients derive a great deal of emotional support from this reassurance. At subsequent office visits an effort should be made to direct the patient's interest into occupational and recreational pursuits that can be handled with his symptomatology. Frequently families tend to become impatient because the patient is slow in performing acts. They must be cautioned against rushing him and must be encouraged to allow him to maintain his feeling of independence, which is reinforced by being able to do things for himself. The patients with parkinsonism frequently become demanding and overbearing and a firm therapeutic hand is necessary to counteract this tendency. No definite rules can be laid down concerning how the emotional problems of each patient should be handled. A practical approach by the physician in dealing with problems as they arise is essential to maintain the maximum improvement.

Against the background of continuous emotional support of the patient, drug therapy can be expected to give an additional 40 to 50 per cent improvement in the patient's symptomatology. A large number of drugs are now available, and often many different drugs or combination of drugs must be tried before the ideal drug therapy is reached for the individual patient. No one preparation is clearly superior to others. The patients may develop a tolerance to medication which has formerly produced a good result and a change in medication may become necessary. A minimum period of six months is necessary before it can be determined whether a drug has a beneficial effect on the symptomatology of parkinsonism. Any conclusion about the efficacy of a drug which has been used less than this length of time is open to a great deal of question. In controlled experiments, we have shown that the psychotherapeutic effect of a change in medication is such that the patient on placebos can demonstrate objective improvement for a period up to five months. Any improvement from a drug maintained after the six-month period is in all probability due to the effect of the drug. The medications currently available will be considered in more detail.

1. Belladonna derivatives. The belladonna drugs are widely distributed in nature, especially in the Solanaceæ plants. Drugs of this group still constitute the mainstay of drug therapy in parkinsonism. The active alkaloids of the belladonna group used in the treatment of parkinsonism are atropine, scopolamine (hyoscine), and hyoscyamine. Tincture of stromonium is used occasionally and contains atropine and hyoscyamine.

The remainder of the drugs of the belladonna group are Bellabulgara, Rabellon, and Vinobel. These compounds contain varying proportions of atropine, scopolamine, and hyoscyamine. Each tablet of Bellabulgara contains .4 mg. of the total alkaloid of belladonna. Rabellon comes in .5 mg. tablets. Each tablet contains .45 mg. of hyoscyamine, .037 mg. of atropine, and 0.012 mg. of scopolamine. Vinobel is manufactured in tablets of 2 sizes: 0.4 mg. and 0.8 mg.

Toxic symptoms. The toxic symptoms encountered in the use of the drugs of the belladonna series are dryness of the mouth; urinary retention; visual blurring; gastrointestinal symptoms such as nausea, diarrhea, and constipation; central nervous system symptoms, such as headaches, dizziness, and in some instances confusion, delirium, and hallucinations.

Mode of administration. Rabellon, Vinobel, Bellabulgara, and, to a lesser extent, hyoscine and atropine are the drugs of the belladonna group which are used most frequently. Tincture of stromonium is of benefit in the occasional case. Atropine is particularly useful when salivation is a difficult symptom to control, and the addition of this drug sometimes produces a gratifying amelioration of this troublesome symptom.

Drugs of the belladonna series are administered initially by determining the maximum dosage that the patient can tolerate and then determining the minimum dosage that produces the maximum therapeutic effect. The latter is the maintenance dose of the drug. Table 1 illustrates the scheme which is used in the administration of Rabellon. A similar schedule is followed when the other drugs are prescribed. It should be noted that the maximum dose of the drug is given before retiring so that if toxic symptoms are encountered, they will occur while the patient is asleep and thus cause a minimum of discomfort. The Bellabulgara and Vinobel tablets are difficult to fractionate and a customary prescription is 1 tablet as an initial dose and 1 tablet every second or third day until a suitable schedule has been worked out. Atropine is administered in a 0.5 per cent solution commencing with 1 drop three times a day and increasing to 10 drops three times a day. Hyoscine administered in tablets of 1/100 gr. or 1/150 gr. is prescribed in a manner similar to Bellabulgara and Vinobel. Tincture of stramonium is started with 20 drops three times a day and slowly increased. The usual maintenance dosage is 60 drops three times a day.

2. Artane. In general, the reactions of Artane (trihexyphenidyl or 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride) resemble those of atropine. However, Artane is entirely free from the toxic effects atropine produces on the cardiac vagus, blood pressure, and circulation. This drug has proved to be a valuable addition to the therapy of parkinsonism and is second only to the belladonna derivatives in the extent to which it is used. In some patients who have oculogyric crises, Artane causes a gratifying improvement in this troublesome symptom.

Mode of administration. When treatment is commenced, 3 of the 2 mg. tablets are prescribed daily. This dosage is increased by 1 tablet every other day until the patient is taking 6 mg. three times a day. The pills are best tolerated when taken after a meal. We have not found it ordinarily beneficial to exceed this dosage. However, in the occasional case, additional benefit is obtained from increasing the dosage. If larger doses are found necessary, it may be well to use the 5 mg. tablet and thus avoid having the patient take a large number of pills. This drug is particularly welcomed by the older age groups because of the low incidence of toxic side effects. After a period of Artane therapy, the addition of a drug of the belladonna series is frequently found necessary, as the effect of Artane appears to wear off when this drug is administered alone.

Toxic symptoms. The toxic symptoms encountered include dryness of the mouth, blurred vision, nausea or vomiting, dizziness or giddiness, drowsiness, tinnitus, tightness in the head, soreness of the mouth, and nervousness or jitteriness. In a small number of patients particularly in the older age group, a serious toxic reaction in the form of a toxic encephalopathy may be encountered. The patients become mentally confused, markedly agitated, and may complain of dizziness with some nausea. We have encountered

TABLE 1
RABELLON SCHEDULE

	Rabellon Tablets—.05 mg. each		
Days	*A.M.*	*Noon*	*Bedtime*
1	¼	¼	½
2	½	½	½
3	½	½	¾
4	¾	¾	¾
5	¾	¾	1
6	1	1	1
7	1	1	1
8	1	1	1¼
9	1¼	1	1¼
10	1¼	1¼	1¼
11	1¼	1¼	1½
12	1½	1¼	1½
13	1½	1½	1½
14	1½	1½	1¾
15	1¾	1½	1¾
16	1¾	1¾	1¾
17	1¾	1¾	2
18	1¾	2	2
19	2	2	2

Increase thereafter by ¼ tablet daily. If any toxic symptoms occur, such as excessive dryness of mouth, dizziness, or blurring of vision, return to dosage of previous day for one week and then attempt to increase again. An attempt should be made to maintain maximum dosage without untoward symptoms.

6 instances of this serious toxic reaction to date, 1 of which terminated fatally. If the patient complains of increased nervousness, a careful watch must be kept to prevent the development of this undesirable serious toxic manifestation. On the whole, Artane has a lower incidence of toxic side effects than the drugs of the belladonna group.

3. Pagitane Hydrochloride. This is a new synthetic drug (1-phenyl-1-cyclopentyl-3-piperidino-1-propanol hydrochloride) closely related in structure and action to Artane. The drug is available in tablets of 1.25 mg. and 2.5 mg. Its mode of administration is similar to that of Artane. Its advantage is that side reactions tend to be less, especially dryness of the mouth and mental clouding, than when Artane is used.

4. Parsidol. This drug (N-(2-diethylaminopropyl)-phenothiazine hydrochloride) was initially introduced in 1949. In some cases which fail to respond to the basic medications, additional benefit may be obtained from the addition of Parsidol.

Mode of administration. The drug comes in 10 and 50 mg. tablets. The dosage is commenced with 10 mg. four times a day and increased by 10 mg. every other day until the beneficial effect is obtained or a dosage of 100 mg. four times a day is reached.

Toxic effects. The toxic effects are minimal and consist of drowsiness and transient giddiness in some patients. The use of Dexedrine in doses of 5 to 10 mg. is useful in relieving drowsiness. The occasional patient complains of transient instances of atropine-like effects and heart burn. Only in a minority, however, must therapy be discontinued because of the side effects of Parsidol.

5. Cogentin. This drug (tropine benzohydryl ether methanesulfonate) has recently been introduced and is of benefit in relieving the tremor and rigidity in some patients with parkinsonism. To date the drug has been added to other basic medications to produce the maximum benefit.

Mode of administration. Cogentin is available in 2 mg. tablets which are quarter scored. The average daily dose ranges from .5 mg. to 2 mg.

6. Antihistaminic agents. The use of Benadryl and Thephorin has been advocated in the treatment of parkinsonism. In our hands, Thephorin has been of no benefit. However, Benadryl, when added to drugs of the balladonna series or to Artane, has produced an additional benefit in some patients. Benadryl is administered in doses of 50 mg. three to four times a day. The sedative effect of the drug is gratifying when the patient is tense. It should be emphasized that if Benadryl is used, it should be used in conjunction with other medications.

7. Amphetamine drugs. Both Benzedrine and Dexedrine are useful in the management of oculogyric crises, mild depressions, somnolence, and lethargy. The usual dosage of either of the drugs is 5 mg. two or three times a day. If the medicine is well tolerated, the dose may be increased to 10 mg. two or three times a day. It is important not to prescribe Benzedrine or Dexedrine after 4 P.M. as administration after this time frequently prohibits the patient from sleeping. Benzedrine and Dexedrine are usually given in combination with other drugs directed toward relief of the tremor and rigidity of parkinsonism.

8. Parpanit. This drug was introduced in 1946 and is an antispasmodic related to Trasentine. Early reports claimed that this drug was more efficient in Parkinson's disease than the atropine-like drugs, but subsequent investigation has failed to confirm these claims. It is worth trying in the occasional patient who has failed to respond to any of the other medications.

Mode of administration. The drug comes in 50 mg. tablets and 1 tablet is prescribed initially with the addition of 1 tablet every second or third day until the maximum therapeutic benefit has been obtained. The average dose ranges between 200 to 400 mg. per day. However, the dosage may range from 100 to 600 mg. per day.

Toxic effects. The toxic effects from this drug occur frequently and are encountered in from 75 to 85 per cent of the patients. The high incidence of toxicity is a relative contraindication to its widespread usage. The toxic symptoms encountered in order of frequency are "giddiness," nausea and epigastric "burning," feeling of lightness of the legs, and a sensation of floating.

9. Tolserol, Myanesin, or Oranixon. Initial reports claimed favorable results after the use of these curare-like drugs (3-ortho-toloxy-1,2-propanediol) in the treatment of parkinsonism. Our experience has paralleled that of subsequent investigators who have found no benefit from the use of these drugs in the treatment of parkinsonism.

Toxic symptoms. Such symptoms are rarely encountered and include nausea, precordial discomfort, complaints of weakness either in the arms or legs accompanied by a feeling of lassitude, and pronounced increase in tremor. The occurrence of 2 cases of leukopenia after the use of these drugs has also been recorded. Early British investigators have recorded the presence of hematuria and hemoglobinuria after their use, but this has not been found by investigators in the United States.

10. Experimental drugs. Dihydro-beta-erythroidine; Dipareol (N-diethyl-amino-ethyl phenothiazine) and Kemadrin are available at research centers and are of additional value in the treatment of some cases of parkinsonism.

PHYSICAL THERAPY

In patients in whom rigidity is pronounced, physical therapy is frequently a useful adjuvant. Mild massage, heat, and directed treatments given one to three times a week may reduce muscle soreness and relax rigidity. Regular visits to the physiatrist afford continuity of treatment and aid in improving the patient's morale. Some of the patients benefit from speech therapy. The purpose of speech therapy is to help the patient speak as intelligibly as possible and to reassure him that his speech is understandable. This can be accomplished by training the patient to speak slowly and to pronounce his words as carefully as possible. It is frequently helpful to have the patient pause after each word or every phrase.

NEUROSURGICAL TREATMENT

No satisfactory surgical treatment is known for parkinsonism. The neurosurgical procedures currently employed are directed toward the cerebral cortex, the basal ganglia, the ansa lenticularis, the cerebral peduncles, or the spinal cord. Only in selected cases, and this constitutes a very small minority, can the victim of this disease be helped by surgical therapy. Even in these cases, surgical measures are never curative and seldom benefit more than one of the many symptoms which are present. Surgical treatment usually substitutes an undesirable neurologic deficit for an even more disabling and disturbing manifestation of the disease.

SUMMARY

1. The nature of parkinsonism is reviewed and a practical classification of this syndrome is presented.

2. Emotional rehabilitation of the patient is of prime importance if the therapeutic regime in parkinsonism is to be successful.

3. In commencing drug therapy in parkinsonism, one of the following drugs is recommended: Vinobel, Rabellon, Bellabulgara, hyoscine, Artane, or Pagitane. A trial of each of these drugs in turn may be necessary or various combinations of the drugs before a satisfactory control of the patient's symptoms is obtained. Additional symptomatic relief can be obtained occasionally by the addition of Parsidol, Cogentin, Benzedrine, Dexedrine, Benadryl or atropine to the previously mentioned medications. In the occasional patient who fails to respond to various combinations of the above medications, the use of Parpanit is worth a trial.

4. Physical therapy is indicated as an adjuvant to treatment if the rigidity is pronounced.

PATIENTS with acute arterial hypertension may sometimes be advantageously treated with reserpine administered intramuscularly. Frank A. Finnerty, Jr., M.D., and James G. Sites, M.D., of the District of Columbia General Hospital, Washington, observed that the medicament induced complete relief from anxiety in 91 of 162 hypertensive and toxemic patients. Blood pressure was reduced an average of 23 mm. Hg systolic and 19 mm. Hg diastolic, an effect which lasted more than six hours. An injection of 2.5 mg. of reserpine is repeated every twelve hours; if no hypotensive effect occurs within two hours or if the condition worsens, 0.5 mg. of purified Veratrum is given intramuscularly. The latter substance or Apresoline may be administered simultaneously in the same syringe with reserpine.

FRANK A. FINNERTY, JR., and JAMES G. SITES: Am. J. M. Sc. 229:379-385, 1955.

Chronic Generalized Edema of Obscure Origin

EARL HILL, M.D.

Minneapolis, Minnesota

Generalized edema of poorly determined origin is probably not a great rarity. Yet the literature concerning such cases is meager indeed. In 1942, Wilson[1] reported 2 cases of transitory generalized nonnephritic edema after respiratory infections. Nuessle and Briggs[2] reported a patient with chronic massive generalized edema, possibly associated with a collagen disease. Jorgensen and Thaysen[3] reported 6 patients with acute cryptogenic edema in 1947 in Denmark, possibly related to an epidemic of glomerulonephritis. Smith and associates[4] mentioned that 3 of 50 edematous patients treated with a cation exchange resin had edema of unknown etiology.

I have studied a patient with chronic generalized edema of obscure origin. Since no explanation can be given for her edema on the basis of prolonged clinical observation and all the presently available studies that can contribute information, a case report is felt worth while.

CASE REPORT

M. H. is a 46-year-old white saleswoman who was first seen in May 1953 complaining of swelling of various parts of the body of three years' duration, gradually becoming worse over this period. The edema was fairly generalized – involving all extremities, the trunk, and the face. The fluid shifted with dependency. She complained that the swelling caused a distended feeling, slowed her, and caused dyspnea when climbing stairs. Her weight increased 20 lb. in the three-year period.

The only endocrine medication taken was thyroid extract for the first four months of 1953 without effect on the edema. She had migraine headaches at the age of 13 which ceased at the age of 45. She denied Bright's disease, albuminuria, or hypertension. Past surgery included removal of the left ovary and half of the right for follicle cysts in 1946. Dilatation and currettage was done in 1952 for prolonged menstrual bleeding.

Family history was noncontributory. She had 2 children, aged 25 and 23. Menstrual periods were on a forty-two-day cycle prior to her pregnancies and on a twenty-one to twenty-four-day cycle after the pregnancies. She was still menstruating irregularly at the time of this report.

Her diet was well balanced and contained adequate protein of both animal and vegetable origin. She added no salt to her food since onset of the swelling, but she did not maintain a salt-free diet.

Physical examination revealed an alert, well developed woman. Her height was 62 in.; her weight was 139 lb. without clothes. The blood pressure was 156/90. Blood pressure readings in subsequent months were at the upper limits of normal with the diastolic pressure varying between 80 and 90. Generalized mild pitting and nonpitting edema was present involving the eyelids, face, trunk, and all extremities. There was no evidence of serous effusions. The only other finding was a mild diffuse enlargement of the thyroid gland which had been present at least seven years.

Urine and hematology. Urinalyses showed specific gravities as high as 1,027. The urine was repeatedly negative for albumin and sugar. The sediment was repeatedly negative for casts, red, or white cells. An Addis count on a twelve-hour catheterized specimen showed 1,600 casts, 1,200,000 white and epithelial cells, a normal number, and 1,600,000 red cells, probably normal.

The hemoglobin was 12.5 gm., the white count 9,300. Differential count showed 51 per cent neutrophils, 46 per cent lymphocytes, 1 per cent monocytes, 2 per cent eosinophils. Subsequent hemoglobins were 14.2 gm. and 13.5 gm., white counts 5,150 and 4,750; another differential count showed 69 per cent neutrophils and 29 per cent lymphocytes. Kline test was negative. Sedimentation rate was 20 mm. in one hour (Westergren).

Plasma proteins and electrolytes. Plasma proteins determined by the salting out method were 7.1 gm. per cent total, albumin 4.1 gm., globulin 3.0 gm., composed of 1.0 gm. each of alpha, beta, and gamma globulin. Plasma proteins by paper electrophoresis showed 8.1 gm. per cent total, of which the albumin was 3.8 gm., alpha$_1$ globulin 0.2 gm., alpha$_2$ globulin 0.4 gm., beta globulin 1.5 gm., and gamma globulin 2.2 gm.

Plasma chlorides were 110 mEq. per liter, serum sodium 155 mEq., and serum potassium 3.5 mEq. per liter. The carbon dioxide combining power was 28.6 mEq. per liter. Six months later the plasma chlorides were 109 mEq., the serum sodium 143, and serum potassium 4.1 mEq. per liter.

Renal function. Blood urea nitrogen was 6.7 and 6.1 mg. per cent on 2 occasions. Phenolsulfonphthalein dye excretion was 30 per cent at fifteen minutes, 59 per cent at thirty minutes, 61 per cent at sixty minutes, and 92 per cent at two hours.

Liver function. Serum bilirubin at one minute was 0.0 mg. per cent, total was 0.6 mg. per cent. Cephalin flocculation was 1+ at twenty-four and forty-eight hours. Bromsulphalein retention was 7 per cent at forty-five minutes.

Thyroid function. Basal metabolic rate was–14 per cent on 2 occasions; serum cholesterol was 295 mg. per cent (normal 140 to 300). Radioiodine thyroid uptake was 41 per cent at twenty-four hours.

EARL HILL, *a 1943 graduate of the University of Minnesota Medical School, practices internal medicine in Minneapolis.*

Other endocrine function tests. Kepler water test was normal. One of the day specimens exceeded the volume of the night specimen fivefold. Thorn test showed 50 eosinophils per cu. mm. basal, and no eosinophils four hours after 25 mg. of ACTH was given intramuscularly.

Cardiac function. The electrocardiogram was repeatedly normal. Chest x-rays and fluoroscopy showed the heart to be normal in size, contour, and pulsations. No evidence of constrictive pericarditis was found. The venous pressure in the antecubital vein was 5 cm. Circulation time from arm to tongue was ten seconds.

Her edema can be decreased but not abolished by nonspecific measures such as mercurial diuretics and cation exchange resins. On a low-salt diet and these medications, she still has generalized edema at all times.

DISCUSSION

All the readily obtainable laboratory tests which might elucidate the etiology of the patient's edema have been done and do not reveal the cause. The elevated serum sodium and chloride suggest an endocrine factor but do not localize it. The cessation of her migraine, a state which is known to be associated with fluid retention in some cases, at about the time the generalized edema developed during the menopausal period suggests a possible connection of these events to changes in estrogen and progesterone secretion.

The only type of edema regarded at present to be due to alterations of ovarian hormone secretion is the cyclic premenstrual edema. An increase in the ratio of estrogen to progesterone is presumed to occur.[5] The direct effect of these hormones individually on fluid retention is insignificant but shift in their ratio seems to activate production of mineralo-corticoids or antidiuretic hormone, or both, resulting in fluid retention.

The fact is well known that renal factors are a common determinant in the common causes of generalized edema.[6] Recent studies prove that the defect consists of excessive reabsorption of salt and water by the renal tubules. The mechanism responsible, which is not fully identified, probably applies to cardiac, nephrotic, and cirrhotic edema alike. They are characterized by renal retention of salt and water and the same renal mechanisms are operative in varying degrees in all 3 conditions. Certain hormonal influences appear to be the likeliest cause. An increased activity of adrenal steroid salt retaining hormones has been demonstrated. These mineralo-corticoids are highly active in promoting reabsorption. Desoxycorticosterone has been known to be the most potent salt retaining steroid. Recently aldosterone, an adrenal steroid 20 times more potent in its salt retaining activity, has been isolated from human blood and urine.[7,8] Aldosterone may be the active principle responsible for increased tubular reabsorption.[9,10]

In the light of this more recent knowledge on the probable alterations in physiology which underlie the development of generalized edema, the trigger mechanism of this patient's edema might be determined if appropriate hormonal assays were available. Mineralo-corticoid assays and antidiuretic activity of body fluids would be most desirable. Estrogen and progesterone levels might also shed light on the mechanism. Even without hormonal assays, it seems fair to assume her edema is due to hormonal alterations.

Presuming that an alteration in one or several of these hormonal activities is demonstrated, the basic cause of her edema, as for most cases of edema in clinical medicine, awaits further research.[9,10] But with the discovery of aldosterone, the ultimate common denominator of the various types of edema is now at least in sight.

SUMMARY

A case of chronic generalized edema of obscure causation is presented. Prolonged observation and laboratory tests do not elucidate the cause.

Present knowledge indicates that the common types of generalized edema—cardiac, nephrotic, and cirrhotic—are due in varying degrees to increased renal tubular reabsorption of sodium. Increased activity of mineralo-corticoids and, less likely, of antidiuretic hormone may well be the basis of the increased tubular reabsorption. Aldosterone, the most potent mineralo-corticoid, may be an important factor in the causation of several types of generalized edema.

The trigger mechanism of the generalized edema in this patient might be clarified if assays for the above hormones could be done. The conclusion is that this patient's edema is probably due to hormonal alterations.

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Changing Concepts in the College and University Student Health Program

GEORGE X. TRIMBLE, M.D.

Columbia, Missouri

THE PRACTICE of student health medicine as it has developed in the college and university student health service has come of age within recent years and now assumes major stature, standing at a professional level comparable to other fields of medical endeavor such as military medicine and industrial medicine.

My reference to industrial and military medicine is not accidental, for these areas of medical practice, like student health medicine, deal with the concept of the healthy mass and pursue the epidemiology of health in dynamic fashion, with the student health program emphasizing in particular the educational aspects of the areas in which it functions.

The cultural, economic, and scientific advances of the past few decades have also brought with them, perhaps I should say forced, a return to a holistic point of view concerning disease. As Dr. Walter Martin, former president of the American Medical Association, so ably stated, we have come to "realize that medicine is something more than the cold application of science to human disease. Medicine is a healing art. It must deal with individuals, their fears, their hopes, and their sorrows. It must reach back farther than the disease that the patient may have, to those physical and environmental factors that condition the individual for the reception of a disease." These ideas, of course, embrace the concept of social medicine.

Those of us who work in the field of student health medicine have appreciated and preached this concept for years, and my contention is that in no area has this concept been more fully evolved and firmly established than in the practice of student health medicine, the scope of which includes not only therapeutic medicine and preventive medicine, but, as I have indicated, social medicine.

Those of us who deal with university students are compelled to take note and evaluate the role that many factors may play in the development of their illnesses. So when the ill student enters our office we find, more often than not, that it is wise for us to be aware of his living habits, his social commitments, his financial resources, his recreational activities, his academic grades, his relations with his girl friend, his family relations, and so on. Disturbances in any of these areas may not only precipitate the student's visit to the health service, but indeed, even before he pays his formal visit to the health service, disturbances in these areas may be a warning signal to his teacher that something is brewing inside the student.

With these few introductory remarks I should like to proceed to call to your attention the fact that the student health service, as we recognize it today, first saw the light of day in the middle of the nineteenth century when President Stearns of Amherst College felt that there was need for colleges and universities to establish programs to protect the health of their students. From these humble beginnings the development of student health services has been truly remarkable, especially so during the years after World War II when college and university student enrollments increased so greatly.

I believe that in keeping with this development the student health service has evolved into an integral and fundamental instrument functioning in the field of preventive medicine and public health. Consequently, the student health service should be and is recognized as a fertile area for the application of many of the accepted technics of preventive medicine and as a worthwhile proving ground for the application of others.

Time will not permit me to mention more than a few of these technics. Nor shall I be able to elaborate upon any beyond mentioning some of the changes in thinking that have occurred in recent years with respect to some of the technics.

The physical examination is one of these fundamental technics. Physical examinations are

GEORGE X. TRIMBLE, *a 1938 graduate of the University of Toronto Faculty of Medicine, is director of the University of Missouri Health Service.*

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conducted in the student health service in connection with a variety of programs.

An entrance physical examination is required of all new students by many universities and colleges. Although routine physical examinations may at times be viewed as drudgery by the examiners, the potentialities that exist in detection of congenital anomalies amenable to surgery have indeed increased tremendously in recent years. A case of patent ductus arteriosus diagnosed initially on entrance physical examination at the Washington University Health Service and successfully treated with surgery was a great source of satisfaction to the personnel who dealt with the case.

In conjunction with the entrance examination, a tuberculosis case-finding program is usually in effect. Many schools require chest x-rays of all new students and pursue comprehensive programs including annual skin testing and follow-up roentgenograms.

BCG vaccination programs have been introduced at some schools for the so-called special risk student groups, such as nurses and medical students. Some schools have felt it worth while to conduct as part of the entrance physical examination special screening examinations for diseases such as diabetes.

Venereal disease case finding has in the past been carried out by means of routine serologic tests for syphilis at the entrance physical examination. In recent years, venereal disease case finding has been felt to warrant little, if any, active prosecution in a university student population, and, as a result, many schools no longer require a routine serologic test for syphilis of new students. This, of course, is in keeping with the pronounced decrease in venereal disease in the United States in recent years.

Pre-employment physical examinations are conducted by the health service of schools which have such a program in effect for their faculty and employees. The performance of yearly executive physical examinations, a feature of many industrial health programs, is under consideration by some schools.

We should take note of the health physics programs in effect at some schools. With the great activity in the field of the so-called "atomic energy" and with the great increase in the numbers of university personnel working with atomic piles and radioactive isotopes, programs set up to help safeguard the health of such personnel have become essential. The health service of Washington University, St. Louis, Missouri, has pioneered in respect to the development, a number of years ago, of a comprehensive health program including yearly ophthalmologic examination and very careful account of all radiation exposures to which the workers have been subjected. This program was developed as a result of the cooperative efforts of various departmental chairmen and representatives in the university, namely, physics, roentgenology, hematology, health service, preventive medicine, pathology, and ophthalmology.

The maintenance of a program in industrial medicine is a health service function in a number of universities. In many schools the health service is responsible for the care of employees injured on duty and for the investigation of any hazards which might exist in this regard. In some schools the health service participates in the planning of extension programs in industrial medicine and hygiene.

The administration of immunizations is a basic function of the health service program. Many schools require smallpox vaccinations of all new students. They also make available other immunizations which are so much in demand in connection with overseas travel. Since World War II, university students have been visiting Europe and other parts of the world in large numbers both for vacation and for study purposes.

A number of university health services, namely, the University of Missouri and the University of Minnesota, have been designated by the United States Public Health Service as vaccination centers.

The supervision of sanitation conditions in the university community is a responsibility of its health service. The areas included in this supervision are university residence halls, dormitories, eating facilities, and off-campus student housing.

This activity often functions in cooperation with officers of the dean of students' division and, in some instances, sanitary engineers form a part of the staff which is responsible for this program.

Mental health or preventive psychiatry is assuming more and more of an important role in health service activities. The experience of most colleges and universities is that emotional and personality difficulties constitute a major and a seemingly increasing problem with a significant segment of the total enrollment of the school. The pronounced increase in foreign student enrollments and the uncertainties which face our own students concerning military service have been considered to be contributory factors. In any event, within the past few years, great demands have developed for mental health facilities. Many universities now provide psychiatric

and clinical psychology counselling services in their health services.

I have touched on but a few of the activities of the health service program. Others, such as research, the disposition of students with special health problems, health and accident and other types of insurance plans are some of the others which time permits me only to mention.

To those of you who are clinicians and internists, I want to extend an invitation to come to the student health service as the place where the answers may be found to the etiology of peptic ulcer, of hypertension and of coronary disease; and where the cure for dysmenorrhea, upper respiratory and other simple viral infections may some day be discovered.

In conclusion, I would like to say that if I have left you with but some indication of the wide scope of student health practice I will have achieved my purpose. Medicine recognizes the specialties of pediatrics and, more recently, geriatrics. I now give you the specialty of hebiatrics, a term coined by Dr. Ralph Canuteson, of the University of Kansas Health Service, from the Greek word for youth.

DISCUSSION

DR. ROBERT E. SHANK, chairman, department of preventive medicine and public health, Washington University School of Medicine, St. Louis, Missouri: Dr. Trimble has reviewed the opportunities available in university health services.

It seems to me that one of the larger opportunities available is for health education and the best use of medical facilities for this purpose. Actually, I think our better university health services are making a real effort to use their facilities and their contacts with students to accomplish this aim in a very effective way. Moreover, a number of universities are utilizing the opportunity that resides within the university health service to gain information of an epidemiologic type. Dr. Moore and his associates at Cornell have had the early evolution of obesity under investigation in the student health service. By such means, very pertinent observations have been made which contribute to knowledge of the natural history of disease.

In a health service with which I have association we have gathered information concerning changing morbidity due to tuberculosis. Just six years ago, about 40 per cent of our students entering medical school were tuberculin positive. About 30 per cent more converted during their four years in medical school. Today, only half that number, or about 20 per cent, are tuberculin positive at the time they enter our first year class, and a smaller number are converting during the period of training in medical school. This observation is important and wholly in line with what we know from other data relative to morbidity due to this disease.

Another study currently going on concerns the etiology of peptic ulcer, which is being followed by a urine test for uropepsin, an enzyme elaborated by the mucosa of the stomach. We know that in patients with peptic ulcer, the activity of this enzyme in urine is markedly increased. By surveying a large group of university students, we have been able to select a small group without symptoms of peptic ulcer who, nevertheless, show high urinary uropepsin. This group is being followed in terms of stresses in university life in an effort to see how these emotional factors influence this manifestation of the disease.

Thank you.

INDIA's tuberculosis problem is gigantic. Probably there are at this moment in India about two and one-half million open infective cases of tuberculosis, and it is estimated that it kills 500,000 people, most of them in early adult life, every year. . . . the total cost to the country comes to around 1,250 million hours of work lost every year because of this disease. — DR. C. MANI, director, WHO regional office for S. E. Asia.

Reserpine and Alseroxylon Therapy in Emotionally Disturbed Patients

ROBERT L. MELLER, M.D.

Minneapolis, Minnesota

The belated trial of Rauwolfia serpentina in this country, in the treatment of both hypertension and mental illness, points up the almost naive incredulity with which many of us are inclined to regard centuries-old medical practices of the East. Continued reports of successful Rauwolfia therapy by modern authoritative workers in India[1–8] seem at last to have penetrated this wall of skepticism sufficiently to initiate scientific investigation.

In the studies of hypertensive patients, the observation that Rauwolfia produced a tranquilizing effect served to encourage therapeutic trial in mentally disturbed patients. That many of us are astounded by the dramatic results obtained with Rauwolfia can perhaps be attributed to the long list of failures in the treatment of mental illness with hypnotics, barbiturates, and other drugs. Discouragement with drug therapy has led to fuller acceptance of the theory that the mentally disturbed can be benefited, if at all, only by psychotherapy and electroshock therapy. Recent studies demonstrate that some patients can be improved or even made symptom free without psychotherapy and that in a good number of cases psychotherapy can be considerably facilitated by the adjunctive use of Rauwolfia.

The percentages of successful results reported in this country, not only in the mentally ill but in the mentally retarded,[9,10] appear to be greater than those reported in the Indian literature. The explanation may be that the whole root, rather than refined alkaloidal extracts, has been largely used there. Most of the studies in this country have employed reserpine, which has been demonstrated to be one of the chief active alkaloids in Rauwolfia serpentina.[11–13]

In the series herein reported, both reserpine (Serpiloid) and alseroxylon (Rauwiloid) were employed, for comparative study. Known potent alkaloids in Rauwiloid include reserpine (trimethoxy benzoic acid ester of methyl reserpate) and rescinnamine (trimethoxy cinnamic acid ester of methyl reserpate). In order to permit evaluation of the pharmacologic properties alone, every attempt was made to eliminate positive suggestion to the patient that treatment with the drug would be beneficial. To this end, even negative suggestion was employed, such as periodic comments to the patient that the improvement he reported might well be transient, due to wishful thinking, or the result of other extraneous factors. An attempt was made, also, to eliminate positive effects of the physician-patient relationship by reducing the length of the office visit to a minimum. In addition, the patients themselves were not optimistic about the outcome of treatment. Their prior comments usually indicated that, because of lack of improvement from other medicaments, they anticipated no benefit from the new drugs.

The series was comprised of 34 patients, 23 women and 11 men. Their ages ranged from 24 to 63 years (table 1). There were varieties of presenting complaints (table 2) with duplication of complaints in many cases. In addition to the presenting complaints, 1 patient was hypertensive and had arteriosclerosis, and 1 suffered from severe arthritis. Neurologic and physical examination disclosed no abnormalities in the remaining 32 patients.

All the patients had been referred, with the diagnosis of psychoneurosis, by other physicians after unsuccessful treatment with various drugs, including barbiturates. In a number of the cases, psychotherapy had also been tried without success. In no case had there been a previous trial with Rauwolfia therapy.

The patients were told only that a new type of drug would be used in treatment, with no discussion of the nature of the drug. Because frequently the number of tablets given was increased or decreased when a change was made from reserpine to alseroxylon, or vice versa, the patients were informed that another drug was being tried. They were not advised when placebos were substituted. Except in the cases in which the patient was unwilling to follow

ROBERT L. MELLER, *a 1938 graduate of the University of Minnesota Medical School, specializes in psychiatry and neurology in Minneapolis.*

TABLE 1
DISTRIBUTION OF AGE GROUPS

Number of patients	*Male*	*Female*	*Age group*
6	1	5	20–30
14	2	11	30–40
7	3	5	40–50
4	3	1	50–60
3	2	1	60–70

TABLE 2
PRESENTING SYMPTOMS OF 34 PSYCHONEUROTIC PATIENTS*

	Number of Cases		*Number of Cases*
"Jitteriness"	30	Infanticidal compulsions	1
Insomnia	24	Suicidal compulsions	1
Anxiety	13	Generalized neurotic compulsions	1
Depression	8	Alcoholism	1
Tension†	6	Difficulty in swallowing	1
Headaches	5	Shoulder pains	1
Fatigability	4	Neurodermatitis	1
Anorexia	2	Epigastric pain	1
Maniaphobia	2	Hypertension	1
Indecisiveness	2	Arthritis	1
Severe tics	2	Numerous phobias	1
Posterior cervical pain			
General discomfort	2		
Limb pains			

*In 1 case there were numerous somatic complaints (not tabulated).
†In several cases manifested by "tightness in head."

through, the time of change-over from one agent to another was determined by (1) relief of symptoms, (2) lack of further improvement from increased dosage, or (3) development of side actions.

REPORT OF CASES

Of the 34 cases, 8 are reported in some detail. These are representative of the series.

Case 1. D. I., a 35-year-old salesman, had been troubled for many years by pronounced feelings of anxiety associated with "tightness in the head" when confronted with even moderately difficult situations. He was also disturbed by chronic indecision and occasional periods of depression.

Reserpine therapy, 0.5 mg. twice daily, was started. The patient reported no benefit after two weeks, at which time the dosage was increased to 0.5 mg. three times a day. He discontinued treatment the following week, stating that he was experiencing strange sensations, "as if I had lost control of myself." After a week without medication, he was persuaded to try Rauwiloid. He reported no benefit the first week while he was taking 4 mg. at bedtime. The dose was then increased to 8 mg., and a week later he stated that he could not remember ever having felt so relaxed and comfortable. He was unwilling to submit to any changes in this regimen, so there were no further trials with varied dosage or with placebos.

Case 2. W. E., a 56-year-old housewife, complained of insomnia, anorexia, and pronounced tension to the extent that she constantly struggled against the impulse to scream. She also suffered from aches and pains in her limbs, which, after discussions with her family physician, were attributed to nervous tension.

Initially she was given 0.5 mg. of reserpine twice daily, but, since she complained of the persistent sedative effect, the dosage was decreased to 0.5 mg. at bedtime. The following week she reported a greater sense of well-being, with less tension and pain but with continued feelings of depression. Her symptoms recurred during a trial with placebos but disappeared when reserpine therapy was reinstituted. After a week's trial with 4 mg. of Rauwiloid at bedtime, the patient complained of strange sensations and drawing pains in her head. Cessation of Rauwiloid therapy resulted in disappearance of these complaints. Reserpine was again administered and the patient manifested the same degree of improvement as with the previous course.

Case 3. P. I., a 40-year-old housewife, complained of insomnia, pronounced "jitteriness," and occasional mild anxiety attacks.

Treatment was started with 0.5 mg. of reserpine at bedtime. Dosage was increased after one week to 0.5 mg. twice daily because of lack of benefit. On her next weekly visit she reported that she felt inexplicably and "horribly" strange. This reaction disappeared after one week without medication. Rauwiloid, 4 mg. at bedtime, was given for one week with no improvement. The dose was increased to 8 mg., and definite improvement occurred in one week. The patient stated that she felt better than she had for years—"I'm my old self again." When the dose was increased to 12 mg. at bedtime, she complained of the same strange feeling she had experienced during reserpine therapy. After a week without medication, she was again given 8 mg. of Rauwiloid at bedtime and experienced relief of symptoms. A trial with placebos resulted in relapse.

Case 4. H. N., a 32-year-old housewife, complained of insomnia, mild anxiety attacks when left alone at night, suboccipital headaches and feelings of "jitteriness" of many years' duration.

Reserpine therapy was started with 0.5 mg. twice daily and increased after one week to 0.5 mg. in the morning and 1.0 mg. at bedtime. The patient reported two weeks after the start of treatment that she felt considerably improved; after an additional week, she stated that she felt completely well. A week's trial with placebos led to a return of symptoms. Reserpine therapy again effected improvement. Rauwiloid was then substituted, 4 mg. in the morning and 8 mg. at bedtime. The patient noted no decrease in her state of well-being.

Case 5. O. L., a 32-year-old secretary, complained of "jitteriness," pains in both shoulders, severe fatigue at the end of her day's work, and a facial rash which had been diagnosed as neurodermatitis. X-ray therapy had been prescribed for the skin condition, but the patient was unwilling to undergo such treatment.

Reserpine therapy was instituted, with 0.5 mg. administered twice daily. She reported that she felt better but a "little sped-up." The bedtime dose was increased to 1.0 mg., so that she was taking a total daily dose of 1.5 mg. Improvement was manifested by euphoria, absence of pain, and a decrease in the severity of the neurodermatitis. However, she stated that she felt "so sped-up that I seem to have lost control of myself." After one week of no medication, 8 mg. of Rauwiloid was given at bedtime. In one week the patient was more relaxed but noted a return of pain to a lesser degree than originally. The dose was increased to 12 mg. at bedtime. A state of well-being was reported after one week; pain and fatigue were absent and she was sleeping well. Three weeks later she stated that the feeling of well-being persisted but that she seemed to have lost all initiative. The Rauwiloid dosage was decreased to 8 mg. at bedtime, and two weeks later the patient

reported that she felt completely well with no complaints whatever.

Case 6. B. R., a 50-year-old insurance agent, complained of pronounced "jitteriness," insomnia, and persistent tension. He had pronounced facial tics and a blood pressure of 200/110. (This is 1 of the 2 patients in the series with organic pathology.) The optic fundi showed grade I arteriosclerosis.

The patient was given 0.5 mg. of Serpiloid twice daily. Progressive improvement was exhibited for two weeks. Since there was no further change after the third week, the dose was increased to 0.5 mg. in the morning and 1 mg. at night. The blood pressure reading was 150/90. The following week, with the blood pressure reduced to 140/90, the patient stated that he had experienced such great improvement that he was most eager to see the effects of a further increase in dosage. The morning dose was increased to 1.0 mg., so that the total daily dose was 2.0 mg. After one week he reported that he had not felt so well in years and was now able "to enjoy life." The facial tics were no longer noticeable. Two weeks later his secretary reported that, whereas previously he had been overly conscientious and driving, he was now neglectful of his work and "taking things too easy." The morning dose of reserpine was therefore decreased to 0.5 mg.; the total daily dose was 1.5 mg. After two additional weeks the patient reported a continued excellent sense of well-being; his blood pressure was 145/90 and the facial tics were absent. His secretary stated that he was attending to business in a normal fashion.

The medication was then changed to Rauwiloid, 4 mg. in the morning and 8 mg. at night. When seen a week later, he complained of a burning abdominal pain that was relieved by drinking milk. Reinstitution of reserpine therapy was followed by a gradual disappearance of the gastric complaint. Symptoms recurred after a week's trial with placebos; his blood pressure rose to 155/90 and the facial tics were occasionally evident. Reserpine therapy again resulted in pronounced improvement. Lower doses of Rauwiloid were not tried.

Case 7. M. A., a 54-year-old insurance agent, complained of pronounced "jitteriness," insomnia, and anxiety attacks when he was home alone at night.

Reserpine therapy was begun and definite improvement was noted after the dosage was increased to 1 mg. four times daily. On this regimen, the patient stated that he felt perfectly comfortable and was sleeping well. He had no real anxiety attacks but experienced occasional "uneasy" spells when he was alone at night. The improvement continued during administration of Rauwiloid, 8 mg. four times a day. A week's trial with placebos resulted in a relapse. Reinstitution of Rauwiloid therapy again effected improvement.

Case 8. M. N., a 35-year-old electrical engineer, complained of pronounced "jitteriness," insomnia, periods of anxiety associated with maniaphobia, and persistent preoccupation with his work during nonworking hours.

Considerable reduction in severity of symptoms was effected with reserpine therapy, 0.5 mg. four times daily. He was sleeping well, was able to forget his work most of the time after hours, and experienced only mild anxiety. However, he was now troubled by severe nasal congestion. After a week without medication, during which the presenting symptoms increased in severity and the nasal congestion decreased, treatment with Rauwiloid was started. A dose of 6 mg. at bedtime effected the same degree of improvement as did the reserpine, except that there was far less nasal congestion. An increase of the Rauwiloid dose to 8 mg. resulted in additional symptomatic improvement but also increased the nasal congestion, so that the dose was reduced to 6 mg. A trial with placebos resulted in a return of the original symptoms, which were again relieved with Rauwiloid therapy.

DISCUSSION

In the group studied, 8 patients showed improvement with either reserpine or alseroxylon (Rauwiloid), 11 responded only to alseroxylon, 5 responded only to reserpine, and 10 were unimproved with either agent (table 3). The daily maintenance doses were as follows: for reserpine, 0.5 mg. in 1 case, 0.75 mg. in 1 case, 1.0 mg. in 4 cases, 1.5 mg. in 5 cases, 2.0 mg. in 2 cases, and 4.0 mg. in 1 case; for alseroxylon, 6 mg. in 3 cases, 8 mg. in 7 cases, 12 mg. in 6 cases, 16 mg. in 1 case, and 32 mg. in 2 cases. Over-all results were from good to excellent. Total success was a little better than 70 per cent. Although this is an impressive percentage, the possible results if therapeutic positive suggestion had been employed are interesting speculations.

The dramatic improvement in the neurodermatitis in case 5 must be attributed directly to alseroxylon therapy. Positive results in cases of psychogenic skin disorders have been noted previously by other authors.[14,15]

Alseroxylon was effective in more cases than reserpine (table 3) and elicited unpleasant side effects less frequently (7 cases) than reserpine (17 cases). It is not clear, at present, why 1 patient manifests a side reaction to alseroxylon but not to reserpine, and another manifests a side reaction to reserpine but not to alseroxylon.

With both alseroxylon and reserpine therapy, a few days elapsed before the effect of the drug was manifested and several days of continued effect after administration of the drug had been stopped. Since the patients were seen weekly,

TABLE 3

SUMMARY OF RESULTS IN 34 CASES OF PSYCHONEUROSIS

No. of patients	*Male*	*Female*	*Response*
9	2	7	Adequate response to alseroxylon
2	1	1*	Moderate response to alseroxylon
4	2†	2†	Adequate response to reserpine
1		1	Moderate response to reserpine
8	2	6	Adequate response to either drug
10	4	6‡	Responded to neither drug
34	11	23	

*Improvement is listed as moderate for this patient, but evaluation was felt to be incomplete since intercurrent infection caused the patient to discontinue alseroxylon medication after only a short trial.

†In 1 male and 1 female patient, individual circumstances prevented trial with alseroxylon. Had they completed the study, it is possible that those patients might have responded well to both drugs.

‡In 1 of these patients, trial with each drug was too short to permit fair evaluation, and, in another, previous psychotherapy and electroshock therapy had been totally without benefit.

the effects were usually not reported in shorter intervals. In every case in which improvement was effected with either drug, a trial with placebos without the patient's knowledge resulted in relapse, which was also usually reported after administration for a week.

Results in this study suggest that the dosage usually recommended for hypertension is insufficient for the treatment of most mental disturbances, particularly anxiety states.

CONCLUSION

Both reserpine (Serpiloid) and alseroxylon (Rauwiloid), in adequate dosage, are capable of altering the psychic state. Alseroxylon appears to be effective and more easily tolerated in a greater number of cases than does reserpine.

The better than 70 per cent success obtained in this series of 34 psychoneurotic patients, without positive suggestion or psychotherapy of any type, suggests that even more dramatic results are obtainable in emotionally disturbed patients by means of adjunctive therapy.

The reserpine (Serpiloid) and alseroxylon (Rauwiloid) used in this study were supplied by Riker Laboratories, Los Angeles, California.

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Treatment with chlorpromazine and barbiturates may prevent or reduce symptoms caused by withdrawal of drugs in narcotic addicts. G. H. Aivazian, M.D., of the University of Tennessee, Memphis, reports that all of 21 drug addicts given this modified sleep therapy were ambulant and asymptomatic within a week and were more amenable to psychotherapy than patients given other regimens. Backache was the only persistent symptom but was alleviated by acetylsalicylic acid. No toxic effects or complications were observed.

G. H. Aivazian: Dis. Nerv. System 16:57-60, 1955.

Neurosyphilis
A Review

HOWARD D. FABING, M.D.
Cincinnati, Ohio

A PRECIPITOUS DROP has occurred in the incidence of all venereal disease in the United States in the last decade. The public health programs in England, France, Scandinavia, and the Germanic countries brought about a striking change of this kind before our own. I remember as a graduate student in London in 1934 listening to an excited group of medical students who had just seen an unusual thing, a chancre, at a time when these lesions were a common occurrence in Cincinnati. The program of the military services during and after World War II, plus the advent of the antibiotics have now made a very real difference in this country too, so that the primary lesion of syphilis is now becoming a rarity among us as well. In recent years, 2 out of 3 syphilis clinics have been closed. A colleague of mine who practices dermatology and syphilology tells me that he has not seen a case of early lues in his practice in the past year.

Some workers in the public health service, however, speak of this as a "fool's paradise." They are alarmed at this relaxation of vigilance before the battle is won. Dr. John Cutler of the United States Public Health Service is credited with the recent statement that in the last year 15 states and the District of Columbia have reported increases in the number of cases of syphilis. It has been estimated that there are still more than 2,000,000 cases in the United States which are either untreated or inadequately treated.

Late syphilis of the cardiovascular and central nervous systems appears to be on the wane, too, but not equally with early infections. The lag period between the invasion of the spirochete and clinical manifestations of syphilis of the nervous system can be unbelievably long, and these cases will continue to appear for diagnosis and treatment for many years whether or not we are vigilant. My prize story in this regard deals with a contractor who fell into a venereal relationship with a maid in his father's house when he was 19 years old. He married shortly thereafter and confined all of his sexual exercise to the nuptial bed from that time forth, according to the report of everyone involved, including his wife. Forty-one years later, after some months of exercising progressively poor judgment in business matters and a series of disastrous plunges on race horses, he began to scrub his teeth with shaving soap every morning, and his wife decided to call the doctor. Paresis was diagnosed. What those spirochetes were doing inside of him for forty-odd years is one of the many riddles which medical science has never solved. Perhaps the disease will die out before a solution is found, but the lesson this man teaches is that many cases of dormant lues will flare into clinical disease before that day arrives.

The clinician was constantly aware of the possibility of late lues in differential diagnosis of central nervous system disease twenty years ago, but now we are more apt to be lulled to sleep by the thought that the disease is diminishing, and we are not as alert as we formerly were about the chance of its being present. I must confess that each time I diagnose a case, I utter a little prayer to Hippocrates to keep me alert. It is well, then, that we review this subject again — lest we forget.

The clinical syndromes involving the central nervous system as the result of luetic infection depend upon the extent of involvement of the parenchyma, meninges, and blood vessels. The combinations are potentially so variable that satisfactory classification is difficult, but, for the sake of clarity, it is well to think of the lesions as consisting of 3 general types: asymptomatic, meningovascular, and parenchymatous.

ASYMPTOMATIC LESIONS

This group is confined to those cases with abnormalities in the cerebrospinal fluid in the absence of clinical symptoms or signs of damage to the nervous system. The central nervous system is apparently invaded by the Treponema pallidum within a few weeks or months after the original infection, since a few patients exhibit pathology in the cerebrospinal fluid in the primary stage, and over one-third of them in the secondary stage. Syphilitic infection which is destined for

HOWARD D. FABING, *a 1932 graduate of the University of Cincinnati College of Medicine, is a specialist in neurology and practices in Cincinnati.*

the heart or the systemic blood vessels does not give the clinician any premonition of the place in which it will strike. However, infection that intends to lodge in the nervous system often leaves a calling card in the cerebrospinal fluid before its visit, as it were, and the neurologist is forewarned in a manner that the cardiologist may envy. Why do some of these infections settle in the nervous system while others do not? This question has never been answered. Neurotropism is more common among white people than among Negroes. The chances of paresis or tabes dorsalis developing are 5 times as great among males than among females. Some authorities contend that one or more pregnancies make the female brain less susceptible to parenchymatous invasion by the spirochete, and, if true, this interesting speculation provokes all kinds of thoughts about the nature of immunity

The thought has also been voiced that some strains are neurotropic and others are not, but experience does not justify this idea. For example, when it was determined that my patient, the contractor, was scrubbing his teeth with shaving soap because spirochetes had invaded the hemispheres of his brain, his wife asked, "What about me?" On clinical examination she proved to be a big, buxom woman in her late fifties in the best of health, but her cerebrospinal fluid had an increase of cells and of protein, the serology was positive, and the gold curve was paretic in configuration. In other words, she had asymptomatic neurosyphilis. She was given artificial fever therapy and a full course of arsenical and bismuth chemotherapy, but her serology remained weakly positive in both blood and cerebrospinal fluid. When penicillin came into use a short time later, this was added. Despite all this therapeutic effort she developed effort dyspnea, a diastolic murmur, Corrigan's pulse, and a cor bovinum. She died with myocardial failure. This woman stated that she had never had sexual relations with anyone except her husband, and except for his affair with the maid, he said that he had been equally chaste. I believed them both. This kind of clinician's data is shaky, perhaps, but the supposition is that the man contracted paresis and his wife luetic aortitis from the maid with spirochetosis. Experiences of this kind, and there are many, make it difficult to believe that such a thing as a neurotropic strain of Treponema pallidum exists, or at least that such tropisms are obligatory.

The treatment of asymptomatic neurosyphilis, which has been called *paresis sine paresi* when the gold curve configuration is paretic, is the same as treatment for the clinical disease. The advent of penicillin has made this a relatively simple procedure. Doses of 15 to 20 million units of penicillin should be given in a fourteen to twenty-one day period intramuscularly and repeated in six months if any laboratory evidence of infection lingers in the cerebrospinal fluid. Aureomycin or Terramycin can be substituted if the patient is sensitive to penicillin. Every patient who has had a diagnosis of early syphilis should have a spinal fluid examination within two or three months after a treatment course, and, to be quite safe, this course should be repeated again in one or two years to rule out the possibility of asymptomatic neurosyphilis gaining a foothold silently.

MENINGOVASCULAR LESIONS

Of the meningovascular forms of neurosyphilis, acute luetic meningitis is the most dramatic. I have seen this disorder develop within months after the primary infection, and, again, I have seen two or three years elapse before it becomes apparent. In this disorder, involvement of the basilar meninges with perivascular infiltration by lymphocytes, plasma cells, and occasional polymorphonuclear leukocytes, and early fibroblastic organization takes place. An inflammation of the ependyma lining the ventricular system also develops. The disorder is usually ushered in by 1 of 3 manifestations: cranial nerve palsies, convulsions and disturbed mental states, or profound headache which may be accompanied by papilledema. Of the cranial nerve palsies, the sixth is common because this nerve has the longest intracranial course and is exposed most to insult by any infectious process. Equally frequent is involvement of the nerves of the cerebellopontile angle, the seventh and eighth, leading to facial palsies and some degree of deafness. Other cranial nerves are involved to a lesser extent. These nerve lesions may be confined to one side or may involve both sides. In the majority of instances, the cobweb thickening of the meninges at the base of the brain interfere with the circulation of the cerebrospinal fluid, leading to increased intracranial pressure which may exceed 400 mm. The papilledema which can occur in this disorder is as severe in degree as any I have ever encountered, and, in the days before penicillin, surgical decompression was often necessary to preserve vision. Inflammatory reaction around the blood vessels leading from the base of the brain may lead to narrowing of the lumen to the point of thrombosis, which leads to confusion, delirium, convulsions, and focal neurologic signs such as hemiplegia and aphasia.

This avalanche of signs and symptoms devel-

oping sometimes within a day and often within a week can add up to a devastating picture of illness, and the differential diagnosis is not easy. The neck is often somewhat stiff, but the patient is not as sick as with purulent meningitis. Thoughts of intracranial tumor or a vascular calamity within the cranium occur to the observer, but the presence of clear cerebrospinal fluid containing 100 to 1,000 cells per cc., predominantly lymphocytes and serologic and gold curve abnormalities, make the diagnosis. The intramuscular injection of a million units of penicillin daily for two or three weeks leads to an end as dramatic as the beginning of this disorder.

Vascular syphilis can occur within the brain as well as anywhere else, but this condition is almost invariably accompanied by a meningeal reaction and an ependymitis. This diffuse chronic involvement of the leptomeninges leads to a complaint of headache and dizziness as a premonitory symptom in at least a quarter of the patients. Rarely, Argyll Robertson pupils may also be present, and, on occasion, cranial nerve weaknesses are noted before the luetic invasion of a nutrient artery in the brain leads to a sudden cerebral accident.

Syphilitic apoplexy is usually not as severe as that caused by arteriosclerosis, and my experience is such that if I were forced to make a choice of vascular accidents in my brain, I should prefer a luetic lesion to an arteriosclerotic lesion, as the better of two bad possibilities. Loss of consciousness is rare with these apoplexies, although onset with convulsion is not infrequent. I remember vividly an elephant trainer who had a right-sided jacksonian epileptic attack followed by aphasia and right hemiplegia. When he was brought to the hospital 20 miles away, his lesion appeared profound and I guessed that he would never see his beloved elephants again. However, within nine months he was back among his animals, using all four extremities and talking fairly well. I know 3 skilled machinists in my city who are back in their shops doing meticulous work after having suffered luetic hemiplegias, and I cannot match that experience with arteriosclerotic accidents. Other experiences of this type (and they may not be consistent with those of my colleagues in neurology) have convinced me that vascular accidents secondary to luetic arteritis of brain vessels are not hopeless prognostically. This is especially true of luetic thrombosis of the posterior inferior cerebellar artery, which has carried a good prognosis for recovery among my patients.

There are 2 meningovascular luetic syndromes involving the spinal cord which should be mentioned. The first is the sudden and dramatic luetic paraplegia which almost always attacks the tenth dorsal segment of the cord. A sudden loss of power and sensation below the navel often occurs on a luetic basis. Formerly this was thought to be the most ischemic portion of the cord, and, therefore, vulnerable. Later anatomic study disclosed that, in most humans, a large nutrient artery joins the cord from either right or left along the posterior nerve root of D_{12} or L_1 and that thrombosis of this artery is responsible for this lesion. Again, the prognosis is not necessarily dismal in this syndrome if the etiology is luetic.

The second site of predilection for meningovascular lues in the cord is the thick part of the cervical enlargement. For some unaccountable reason, luetic infection may settle here, causing a great leathery thickening of the meninges, pinching the cervical nerve roots, and even compressing the cord. Atrophy of the muscles of the pectoral girdle and the upper extremities usually follows. The older literature described many cases of this type to which the resounding Latin name of *pachymeningitis hypertrophica cervicalis luetica* was given, which required surgical exploration for relief, but these cases are now rare.

PARENCHYMATOUS LESIONS

We now come to the parenchymatous forms of neurosyphilis, tabes dorsalis, and paresis. At the outset, it is well to make the general statement that tabes is a clinical diagnosis and that paresis is a laboratory diagnosis. When a case of locomotor ataxia is well developed, the spinal fluid is often quiescent and cannot be relied upon to demonstrate changes in serology, gold curve, protein content, nor colloidal gold precipitation which are diagnostic. A physician is forced to rely upon his eyes, ears, and hands in making the diagnosis. Paresis, on the other hand, continues as an active process to the extent that the spinal fluid is almost 100 per cent reliable as a laboratory confirmation of the clinical diagnosis.

Tabes dorsalis is characterized pathologically by degeneration in the posterior roots, the posterior funiculi of the spinal cord (especially the columns of Goll), and the brain stem. In the early stages, the leptomeninges and the intraspinal portion of the posterior roots are infiltrated with lymphocytes and plasma cells, and, as with all central nervous system lues, usually basilar meningitis and ependymitis are also present. As the disease progresses, these inflammatory manifestations abate, and the so-called "burned out" case has a normal or almost-normal spinal fluid and no inflammatory cellular reaction.

Tabes can be a veritable museum of neurologic findings, but diagnosis can seldom go wrong if the physician adheres to 2 triads. The triad of complaints—lightning pains, dysuria and ataxia, combined with the triad of findings—Argyll Robertson pupils, absent deep reflexes, and loss of proprioceptive sensibility are so characteristic that these conditions lead directly to the diagnosis. For general guidance, tabetics are usually thin individuals.

The pains are worthy of mention. They are seldom like electric shock that run up and down the legs, but are more often described as knife-blade jabs, or the jabs that a packet of needles would make if repeatedly plunged at right angles into one area of the skin of the lower extremities. They jab in one place for awhile, then stop, then jab repeatedly again for as long as a day or two, then jump to another spot (often over a bony prominence), and begin the whole process over again.

The following story sounds impossible, because who ever heard of a mail carrier with a wooden leg? My tabetic mail carrier had severe jabbing root pains in his wooden leg for eleven years. He took it off, tinkered with it, oiled it, and cursed it, but the wooden leg continued to cause pain.

The broad-based wobbly ataxia of the tabetic, with inconstant height of each step, is diagnostic after being impressed on the visual memory. The condition is worse when the eyes cannot compensate for the lack of muscle and joint sense and is, therefore, worse in the dark or when the eyes are covered. The Germans speak of the "waschentisch" syndrome, in which the tabetic falls into the washbowl when his eyes are filled with soapsuds. In reality this is an informal way of performing Romberg's test. The dysuria is that of a relaxed bladder which lacks pushing power, with consequent overflow incontinence in the late stages.

In tabes, the tendons at the knee and ankle even feel relaxed, and, when struck with the percussion hammer, no response is evoked and a dull thudding sound is heard. The triceps jerk is also absent in many cases, but not the biceps and radioperiosteal jerks. Argyll Robertson, in his celebrated paper in 1861, in which he described the pupils which made him famous, described 2 cases of spinal *miosis*. This pupil is small, irregular, fixed to light, and reacts when it accommodates for distance, according to its discoverer. The only thing which has been added in almost one hundred years is that it dilates slowly to mydriatics. This pupil, or variations of it, is the pupil of tabes, and is one of the reliable findings in the disease. The lack of joint and muscle sense leads to flabby, relaxed muscles, and the lower extremities of these patients appear "double jointed." A curious concomitant finding is the delay in pain appreciation in the tabetic. He may wait four to ten seconds to say "ouch" after pinching the skin of his legs or compressing his testis.

Other manifestations such as paresthesias, gastric or visceral crises, rectal incontinence, optic atrophy, deafness, impotence, and Charcot's joints all add themselves to this multiform disorder, but time does not permit us to tarry with them.

The therapy of tabes dorsalis leaves much to be desired. Penicillin in the doses outlined for other forms of central nervous system lues is said to arrest the forward progress of the disease, but this has failed in some cases. Most of the manifestations of this disease are due to scars in the central nervous system, and we are asking a great deal of penicillin or other therapies to eradicate scars. Gastric crises, tabetic optic atrophy, and Charcot's joints sometimes defy the most ardent therapist. Dorsal rhizotomy and vagotomy have failed to relieve visceral crises, and I have abandoned these surgical methods of attack. Massive doses of penicillin concomitant with 14 sessions of artificial fever therapy, totaling forty-two hours of hyperpyrexia, deserve trial because this combined therapy often helps.

Paresis, or general paralysis of the insane, or dementia paralytica usually occur in stocky or fat people, unlike tabes which ordinarily occurs in lanky thin individuals. These body types cannot be relied on, however, since some individuals of any build may have both diseases together, or taboparesis, or either disease singly. Paresis is a chronic spirochetal meningoencephalitis which destroys or severely disturbs the function of the cerebral cortex and leads to a general dissolution of physical and mental capacities. The brain becomes atrophic especially over the convexity of the frontal and temporal lobes. The leptomeninges are thickened, milky, opaque, and adherent over the atrophic areas. Microscopically there is a chronic inflammatory reaction in the meninges and perivascular spaces and degeneration of the parenchyma of the brain and spinal cord. A deposition of iron pigment occurs, and the tenacious Japanese microscopist, Noguchi, taught us how to find the spirochetes throughout the affected areas.

The clinical manifestations of dementia paralytica are, like tabes, usually seen in the fourth and fifth decades of life, and one wonders how many years this chronic infection goes on silently

before it balloons up before the eyes of the observer. In congenital syphilis, infection has been found before the age of 10 years, and I remember a pretty dark-haired 12-year-old girl with far advanced paresis. The disease may simulate any type of mental disorder of the functional or organic reaction type, so that it is a mimic of all types of mental illnesses. It goes through an incipient stage, a stage of full development, and a stage of decline.

The early manifestations are irritability, fatigability, bizarre and often explosive conduct disorders, mild personality changes, headaches, and tremors of the hand and tongue. As the disease progresses and fully develops, memory is greatly impaired, more often for recent happenings; defects in judgment occur, especially in regard to money and amorous ventures; a progressive lack of insight into the nature and extent of the difficulty is noted; moods alter and may be either depressive, or elated and overactive; confusion and disorientation is present; rather feeble delusions take place, usually of a paranoid nature; and overt tremors of tongue, speech, and hands occur. As the disease progresses, seizures of epileptic and apoplectic types begin to occur. The latter are so characteristic that if a patient has a hemiplegia or an aphasia and recovers in a matter of days, paresis should be suspected until proved otherwise. As the period of decline sets in, seizures become more frequent and intellectual defects and paralytic phenomena progress. Finally the untreated patient becomes paraplegic, bedridden, incontinent, and often dies in convulsions.

Although most of the clinical manifestations are in the mental sphere early in the disease, tabetic manifestations, pupillary changes, cranial nerve palsies, Babinski's sign, and speech and handwriting disorders may also be found. I seem to have gathered a series of cases in which diplopia was the presenting symptom in recent practice. Perhaps the most telling sign is the paretic facies. An early muscle which becomes weak and partially paralyzed is the levator of the eyelids. This produces a partial ptosis and a sleepy look. In order to raise the lids, the patient wrinkles his forehead, thus lifting the whole brow and lid as in the expression of surprise. This surprised plus sleepy look is striking to the trained eye, and I have seen old and wise neurologists make the diagnosis from such an expression.

I treat paresis with a combination of penicillin and artificial fever. Some clinicians rely on penicillin alone, but I find this a hard disease to treat, and, in my experience, some patients have had progressive symptoms on penicillin alone.

I should like to leave one thought about paresis. If a physician waits to see the euphoric, expansive paretic who wants to give away a million dollars—the paretic of the older textbooks—he will probably miss the next 20 paretics he encounters. Furthermore, I hope that our knowledge and treatment of early syphilis is now so good that 20 new cases of paresis never occur.

Corticotropin (Acthar Gel) or cortisone has been found to relieve the pain of postherpetic neuralgia. Gordon C. Sauer, M.D., of the University of Kansas, Kansas City, reports that pain was relieved in 14 of 21 patients treated with the drugs and in 7 of 11 persons given placebos. No significant difference in effectiveness of the 2 drugs was apparent.

Gordon C. Sauer: Arch. Dermat. 71:488-491, 1955.

Plastic Blood Vessels Made of Polyvinyl Sponge

NORMAN E. SHUMWAY, M.D., F. JOHN LEWIS, M.D., and MARVIN L. GLIEDMAN, M.D.

Minneapolis, Minnesota

The need for blood vessel substitutes has become so great that artificial grafts are being devised to supply a demand unfulfilled by homografts. The concept of prosthetic arteries is not new, but the circumstances that surround their current introduction are different from those which prevailed years ago when the possibilities of homografts were incompletely appreciated. Homografts have been used effectively, and no question of their suitability can now be raised. Nonetheless, the problem of availability in size and shape cannot be solved by homologous vessels. This fact has intensified research into artificial grafts.

Much work has been done with venous grafts, but the concern of this paper is specifically arterial replacement. Extensive cancer surgery, particularly in the region of the portal vein, makes the consideration of venous prostheses an important matter. Artificial venous grafts are probably more difficult to improvise than arterial prostheses, but fortunately instances where venous substitution is critical are fewer.

Histologic examinations of homografts in animals sacrificed at various intervals postoperatively have revealed that the grafts do not survive as living structures but are merely the framework for adjacent tissue proliferation.[1] This provokes the suggestion that the framework may as well be prosthetic in nature. The expense and elaborate technics inherent in the operation of an arterial homograft bank are reason enough to look elsewhere for vascular substitutes. All too often at the crucial moment a homograft selected prior to surgery either requires extensive tailoring or is totally inadequate. These facts plus the increasing number of aortic resections for aneurysms and occlusive disease bring sharply into focus the virtual necessity for artificial vascular grafts.

NORMAN E. SHUMWAY, *a 1949 graduate of Vanderbilt University, is with the department of surgery at the University of Minnesota and is United States Public Health Service research fellow of the National Heart Institute.* F. JOHN LEWIS, *a 1941 graduate of the University of Minnesota, is with the department of surgery at the University of Minnesota.* MARVIN L. GLIEDMAN, *a 1954 graduate of New York State Medical College in Brooklyn, interned at the University of Minnesota hospitals and is now resident in surgery at Kings County Hospital, Brooklyn.*

PLASTIC FABRIC GRAFTS

In 1952, Voorhees and associates[2] described their success with the experimental use of vinyon "N" cloth grafts for arterial substitutes. Various plastic textiles were investigated by this group which chose ultimately to advocate vinyon "N". A substantial and impressive clinical experience was reviewed by Blakemore and Voorhees[3] in 1954, with the conclusion that vinyon "N" was a satisfactory material for replacing diseased or injured segments of the vascular system.

Shumacker and King[4] recently announced a similar experience with nylon grafts. Initial work was directed toward methods of preventing leakage through the fabric itself after the graft had been sutured into position. Polythene sheeting incorporated between nylon layers solved the problem and made way for successful clinical trial. Braided nylon tubes coated with vinyl plastic have also been found suitable for bridging defects in the aorta of dogs.[5] Such tubes have the characteristic of elasticity permitting expansion with each pulse wave. Whether the property of pulsatile expansion is necessary in artificial blood vessels is still not resolved. Most of the materials used have a greater or lesser degree of elasticity.

Orlon grafts investigated by Hufnagel have been adopted by DeBakey,[6] whose large series of aortic resections for arteriosclerotic aneurysms and occlusive disease has exhausted the available supply of homografts. Some difficulty, however, has been reported in the experimental use of bifurcation prostheses made of orlon.[7] Delayed hemorrhage and so-called "wrinkle thrombosis" have detracted from the over-all good results.

From the department of surgery, University of Minnesota Medical School.

Almost any kind of plastic textile is satisfactory for restoring blood vessel continuity with one or two reservations. The weave must be fine enough to render the cloth blood-tight; otherwise, something must be added to insure a relatively leak-proof prosthesis. A second factor which requires vigilance is related to the hazard of thrombosis when the graft has not been made sufficiently taut. Of course, one wrinkle which cannot be deleted from the fabric graft is the longitudinal, inside seam. Another disadvantage of the cloth graft is its flimsy consistency which presents an unnecessary technical challenge for the suture anastomosis. In view of these real and relative disadvantages of cloth prostheses, we have investigated the use of aortic grafts constructed from polyvinyl sponge, available commercially as Ivalon.[8]

PREPARATION OF POLYVINYL SPONGE GRAFTS

Sheets and strips of polyvinyl sponge are cut from the dry brick with a sharp carving knife. The thickness can vary, but 2 mm. is quite satisfactory. The cut surface of the sponge appears very much like white bread, though perhaps somewhat more porous. Next, the sheets or strips are immersed in cold saline and then wrapped around copper tubing of the size desired for the internal diameter of the graft. In order to provide sufficient overlap to cover all holes in the material, two or three turns around the tubing are necessary. Ivalon is of variable porosity, but, when the texture is fine, two layers are usually adequate. Compression is exerted by means of two aluminum plates molded to fit the tubing. The plates are tightened by means of wires or

Fig. 1. Ivalon sponge brick and sheets and strips which have been cut from the dry brick.

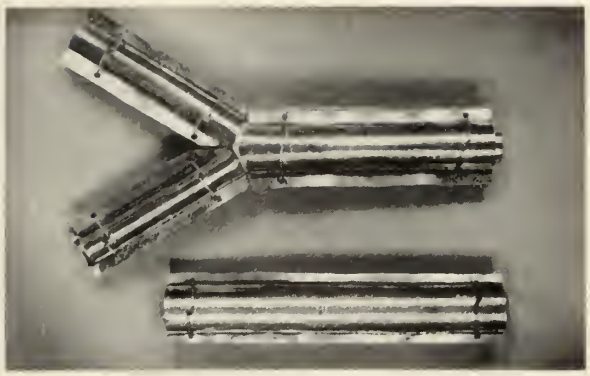

Fig. 2. Aluminum shields enclosing sponge grafts are shown. Molds are ready for boiling in water.

Fig. 3. These are the finished products which can be sutured into position by the same technics employed in ordinary blood vessel anastomosis.

Hoffman clamps, and the entire mold with its enclosed graft is then ready for sterilization. Boiling in water for thirty minutes not only effects sterilization but also fixes the shape which will endure after compression is discontinued and the graft is removed from its aluminum sheath and copper tubing.

Figure 1 shows an Ivalon brick and strips and sheets of the material. Figure 2 is a photograph of the grafts in the molds ready for boiling. The end product is shown in figure 3. Bifurcation grafts are made as described above except for a strip of sponge which is applied at the apex of the Y to insure a good seal at the junction of the iliac limbs with the aortic portion of the graft.

EXPERIMENTAL RESULTS

A detailed analysis of the use of polyvinyl sponge grafts in dogs has been previously reported.[8] In summary, however, several interesting points deserve attention here. Animals sacrificed two months postoperatively showed endothelium completely covering the inner aspect of the graft, while islands of living tissue had penetrat-

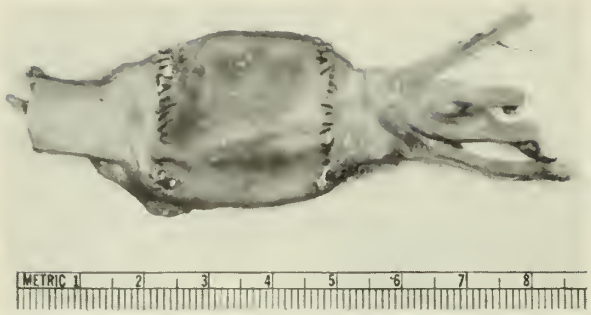

Fig. 4. This specimen was removed from a dog sacrificed at two months after replacement of an aortic segment with the sponge graft. Intimal surface is covered completely by endothelium.

Fig. 5. Posterior view of a bifurcation graft in a human who survived one week postoperatively but died of renal failure unrelated to the graft.

ed into the interstices of the sponge. Figure 4 is a photograph of a specimen removed from a dog sacrificed two months postoperatively. Thrombosis has not occurred, and the graft is covered nicely with endothelium.

The inert nature of Ivalon sponge has been emphasized by its many previous medical uses. A relative lack of leukocytic response to the presence of polyvinyl sponge was noted in the microscopic sections taken from the grafts. Suture anastomosis is easy to accomplish because the texture of the graft is very much like that of normal arterial tissue. Ivalon grafts are resilient and capable of expansile pulsation but have great tensile strength, a fact pointed out early by Grindlay and Waugh[9] who did much to introduce the medical possibilities of polyvinyl sponge. There is no inside seam or wrinkle tendency to predispose to thrombosis. In none of the animals was there any evidence of dilatation, aneurysmal formation, or constriction of the lumen. Only 1 of 14 animals exhibited evidence of thrombosis, and this occurred at the suture line of a bifurcation graft where the iliac limb was less than 5 mm. in diameter. The anastomosis was technically difficult and doubtlessly imperfect. At the conclusion of the experimental work, we felt justified in recommending polyvinyl sponge grafts for clinical trial.

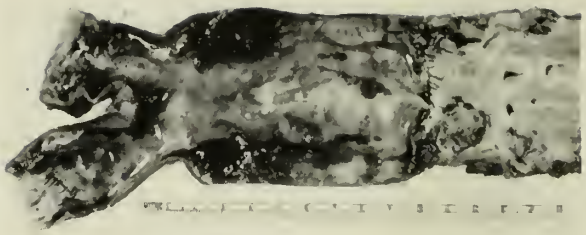

Fig. 6. Anterior view of the same specimen as shown in figure 5 with a thin coat of fibrin on the interior without evidence of thrombosis. Note arteriosclerotic plaques in the aorta above the anastomosis.

REPORT OF A CLINICAL CASE

Figures 5 and 6 are photographs of the specimen taken from a 62-year-old male patient who expired one week postoperatively. The Ivalon bifurcation graft is free of thrombosis, and, while there is no endothelium as yet, a thin layer of fibrin covers the intimal surface. An arteriosclerotic aneurysm of the aortic bifurcation extending almost to the renal arteries was excised at the time of surgery. The cause of death was not related to the plastic graft. Renal failure probably secondary to prolonged occlusion of the aorta was the fatal complication.

SUMMARY AND CONCLUSIONS

1. Plastic blood vessels have been constructed from polyvinyl sponge for use as aortic substitutes.

2. The insufficiency as well as the inadequacy of homografts to meet the expanding need for blood vessel replacement has been cited.

3. The advantages of Ivalon grafts over cloth grafts have been noted.

4. Experimental results have been encouraging, and one clinical case has been reported. Further clinical trial seems clearly to be indicated.

Ivalon is a product of Clay-Adams, New York City.

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(Continued on page 39A)

A New Organic Absorbent Powder Base

Clinical Results in 327 Cases
A Preliminary Report

CLEVELAND J. WHITE, M.D.
Chicago, Illionis

Dusting powders are fine, grit-free preparations intended for application to the skin surface. Powders for this purpose have been in use for many years, have been manufactured along the same general lines, and nothing new has been added for many decades. Powders in themselves have one therapeutic property common to all, which is their protective action. By clinging to the surface, they form a covering that to some extent protects the skin from contact with the air and from the friction of clothing. Thus, itching and burning sensations are lessened. When the skin is not excoriated, a waterproof powder may be useful to form a protection against macerations from secretions of a watery nature. Such powders, because of their physical affinity to fat, cling to and are especially suitable for protecting a fatty surface, such as the normal skin against irritations from watery discharges; for example, the irritation caused by urinary secretions.

After excoriation has occurred and a weeping surface is present, a water-absorbent dusting powder is preferable to a waterproof powder. Water-absorbent powders, because of their force of capillary attraction, are capable of taking up fluid from the skin's surface and thereby exerting a drying action. Moisture is essential for the multiplication of bacteria and fungi. Consequently, some powders of specific fineness can inhibit to a pronounced degree the growth of microorganisms. If powder does not cake, it will cause a drying action and also a certain amount of condensation of tissue which is similar to the effect of an astringent.

Starch has been used as a somewhat effective water-absorbent and also such mineral powders as talcum, chalk, and kaolin. However, starch cannot be employed unless protected by an antiseptic on discharging surfaces because of a decided tendency to decompose. In the past, for such purposes, kaolin or fuller's earth have been used, but usually a 2 to 4 per cent boric acid or 1 per cent salicylic acid has been added to antagonize decomposition in the absorbed discharge. Thus, because of the factors just enumerated, it can be seen that there has been no powder base which in itself heretofore could absorb the moisture either from an inflammatory surface or from areas of pronounced hyperhidrosis. It is apparent that a vegetable, organic cellulose powder base which requires no additive that might irritate is certainly needed. As mentioned previously, powders in the past have had mineral bases which could irritate or even cause absorption and possibly poisoning, for example, boric acid in infants or a vegetable preparation used as starch which, of course, cakes on contact with fluids such as serous or inflammatory exudates of the skin and then decomposes. Therefore, a preparation that absorbs moisture deprives the microorganisms, such as bacteria and fungi, of a medium in which to grow. The inflammatory secretion and macerated exudation can be readily absorbed. As for the few remaining organisms, proper treatment can be instituted on the eroded areas or previously hyperhidrotic surfaces after this pronounced absorption by the powder.

Such a powder has been used in 327 cases, which will be described in groups, and consists of a powdered, specially-processed maize containing vegetable and other organic ingredients. It does not contain starch, as does the seed, but is an organic absorbent. The aim was to try to find a powder base to be used solely for the purpose of absorbing either inflammatory or hyperhidrotic secretions, thereby reducing infection to such a degree that more active fungicidal or bactericidal ingredients could be used. Talcum,

CLEVELAND J. WHITE, *a 1922 graduate of Rush Medical College, is professor and director of dermatology, Stritch School of Medicine, Loyola University, Chicago, Illinois*

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Scientific exhibit, Illinois State Medical Society, May 1955.

which is a fine, white mineral powder, is commonly used either as a base for a dusting powder or as a dusting powder itself. Because of its chemical indifference, it has been a favorite diluent for antiseptic and astringent powders. However, these powders cannot be dusted on extensive, profusely-excreting raw or eroded surfaces because of their tendency to cake and form a thick crust by combining with the desiccation secretions. This caking in turn favors retention of discharge and allows bacteria and fungi to grow. The crust because of its hardness also produces irritation. On very small discrete areas, such a powder could be used, but not on extensive moist areas. All mineral powder bases cake when in contact with serous exudate or excessive perspiration. By absorbing inflammatory exudate, secondary bacterial invasion can be easily checked. Furthermore, if perspiration is excessive, it can be readily absorbed by this cellulose organic base which prevents further fungous infection and easily reduces the moisture of the background so that a fungous reinfection will not occur.

This powder base, consisting of maize and other organic ingredients, in contrast to the aforementioned powders, can be used on extensive surfaces, since it does not cake and absorbs moisture effectively up to almost 5 times its own weight. Crust irritation and decomposition cannot occur. Benedek[1] has pointed out that cellulose cannot be invaded by any known human pathogenic molds or bacteria. Hence, it absorbs the moisture—either inflammatory, exudative, or hyperhidrotic—so that molds and bacteria cannot grow and remains impervious to their promulgation.

The powder base has a *p*H value of 4.3 and, thus, is definitely acidic, which fits into the general scheme of endeavoring to keep or assist the normal glabrous skin to return to "normal" reaction.

Bacteriostatic studies in connection with this powder have been pursued. The number of bacteria have been observed to have been reduced over 90 per cent in thirty-six hours (see addendum). The fungi have been reduced over 87 per cent in forty-eight hours. This new absorptive powder has been used in 6 cases of severe hyperhidrosis with no cutaneous inflammation. It has been used in 294 cases of superficial fungous infection in which excessive hyperhidrosis existed with widespread inflammatory involvement and pronounced exudation. These were found especially in intertriginous areas — the crura, the axillary, and the inframammary and interdigital spaces of the toes. In 89 per cent of these cases, fungi of the Trichophyton gypseum type were isolated; in addition, bacteria (staphylococci) were found in 112 cases; and in 11 per cent, moniliasis was found. The powder was used in 9 cases of widespread exfoliative dermatitis, in 6 cases of pemphigus, in 8 cases of exudative bullous erythema multiforme, and 4 cases of widespread carcinoma of the skin with offensive odor from secondary bacterial infection. In the cases of pemphigus, the powder was used to absorb the moisture in the large raw exudative areas which were very odoriferous. By absorbing the moisture in these cases, the patients experienced symptomatic relief and the condition was almost completely deodorized. Obviously, the progress of the disease was not influenced, but the powder did have a definite palliative effect which was pleasing to the patients and to the nursing personnel. In the cases of exudative bullous erythema multiforme, the powder acted as a moisture absorbent in the large eroded lesions. In the whole series, only 6 patients were too sensitive to tolerate this powder base.

L. E. Gaul has emphasized the prevalence of over-treatment in many cases of dermatoses, especially in the acute phases. This can be prevented many times by absorbing the inflammatory exudate where possible and subsequently using mild preparations to cure the remaining infectious element.

Our clinical results have been very striking, especially with respect to intertriginous areas. A specific example is that of a business executive who had been suffering from a pronounced hyperhidrotic inflammatory condition of the crural areas which produced a pronounced infectious syndrome with some fungi and especially bacteria, causing elephantiasis of the genitalia. This condition had persisted for several years, and had incapacitated the patient for several months at a time during the past three years. He had been treated by numerous dermatologists and at various clinics. The powder absorbed the excessive moisture to the extent that the elephantiasis subsided to normal in four days. Then, by use of fungicidal preparations in both the groin and the feet, in addition to the powder to absorb the moisture, the condition completely cleared. He continues occasionally to use this preparation when the perspiration becomes somewhat pronounced.

In pronounced hyperhidrosis with accompanying odor, the powder has been of great help in absorbing the moisture which deprives the bacteria of a medium for growth, which, in turn, produce odor. This has been especially true in

pemphigus, exfoliative dermatitis, and secondary infections in widespread cancer of an ulcerative nature. The preparations which have been used after the reduction of the hyperhidrosis and inflammatory exudates will be treated in detail in other publications.

SUMMARY

A new organic cellulose powder base has been used with great therapeutic efficiency in pronounced inflammatory or hyperhidrotic states to reduce the growth of bacteria and fungi by the absorption of excessive moisture. After this is accomplished, the residual infectious condition can be more effectively treated by other specific medicaments. Another essential feature of this powder is its deodorizing effect which is caused by the reduction of moisture in which surroundings bacteria thrive, producing the obnoxious odors. This is the first addition for many decades of a new powder base for use on cutaneous diseases.

ADDENDUM

In taking cultures from 17 powders alleged to prevent athlete's foot, which were purchased over the counters in various stores, 15 were found on Sabouraud's media and blood agar to grow molds and bacteria. Some, however, were in the Aspergillus group, and whether all of this group are pathogenic is questionable, although they may be. The Candida albicans were grown in a few instances as well as bacteria of the staphylococcus type (on the blood agar). Since these powder preparations contained fungicidal or bactericidal ingredients, probably the positive cultures were grown on the powder base itself. Therefore, in view of these findings, some of these preparations could conceivably cause infection in sensitive or irritated skin.

The new powder base has been found negative on culture for both molds and bacteria over a period of seventeen successive months; that is, since the time of sterilization.

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Urinary tract infections may be effectively treated with nitrofurantoin (Furadantin) administered orally in a daily dosage of 4 to 14 mg. per kilogram of body weight. Howard M. Trafton, M.D., of Tufts College, Boston, and associates find that most strains of *Escherichia coli, Aerobacter aerogenes,* and *Streptococcus faecalis* are eradicated by the medicament but that strains of *Pseudomonas aeruginosa* are not affected. Improvement was obtained in 30 of 36 patients with chronic disease and in 12 of 13 instances of acute, subacute, or postoperative infection. Untoward effects were observed in 15 of 60 patients. Tolerance to the drug diminished in 4 of 11 persons given more than one course.

Howard M. Trafton and associates: New England J. Med. 252:383-387, 1955.

Presidential Address at the Annual Meeting of the American College Heath Association

NORMAN S. MOORE, M.D.
Ithaca, New York

A CUSTOMARY EVENT at meetings of American professional societies is the traditional president's address. Some associations expect the president at the annual meeting to sum up the association's past accomplishments, adding his own administration's contribution to those of his predecessors. A perusal of many addresses of past presidents of this society leads me to believe such is the tradition with this association. Nevertheless, I feel I must part from tradition, for the history of student health has been told so thoroughly by so many persons that what I might add could be of little interest.

Instead, I beg your permission to depart from tradition and to discuss the lessons learned from past experience which, if heeded, in my opinion, could very well influence the future rate and degree of development of student medicine. Also, please permit me to comment on the possible roles we could play both as an association and as individuals.

From the past we have learned that a proper balance between health education and clinical care is essential if we completely discharge our medical obligations to students. We have learned that our obligations include more than health instruction, preventive medicine, sanitation, and control of communicable disease. We have been made mindful of the fact that we need manpower having clinical judgment commensurate with the rapid scientific changes medicine is undergoing. We have learned, too, that physicians should preserve their skills by restricting their professional activities primarily to medicine, delegating many of the nonmedical counseling duties to colleagues trained in those fields. The development of counseling and personnel services in American institutions of higher learning has focused the attention of faculties and deans on the needs of the individual student. If the health service is to achieve its aim of helping the student understand and establish principles of health conservation, there must be a close working relationship between the physician and all other departments of the college or university. We have learned that in this relationship, the physician retains more respect and prestige if he remains the doctor on the team without necessarily assuming the dominant role. Out of our studies of the reasons for student academic failures, we have learned to understand the problems of workers in other disciplines and to appreciate that the successful student-medical worker at every level must integrate his knowledg with that of his many academic colleagues.

Another lesson we have learned from the past is that isolation leads inevitably to deterioration and boredom which wreak havoc with our determination and ability to do the job well. While student medicine does offer a career less strenuous than the general practice of medicine, nevertheless such a career bathed in the intellectual vacuum of indifference is not the answer to America's university and college students' medical needs. Osler verbalized the danger of deterioration so well in his famous address on chauvinism in medicine that I quote the master rather than attempt to express it myself. Speaking of the general practitioner he said, "To make him efficient is our highest ambition as teachers, to save him from evil should be our constant care as a guild . . . Few men live lives of more devoted self sacrifice than the family physician . . . There is danger in this treadmill of life lest he lose more than health and time and rest . . . his intellectual independence. More than most men he feels the tragedy of isolation . . . The peril is that should he cease to think for himself, he becomes a mere automaton, doing a penny in the slot business which places him on a level with the chemist's clerk who can hand

NORMAN S. MOORE, *past president of the American College Health Association and member of the executive committee, is with the student health service at Cornell University, Ithaca, New York.*

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out specifics for every ill, from the pip to the pox." [1]

What a true and vivid description of the pitfalls of student medicine with its burdensome repetition of minor ills; and how easy for automatism to rule and block understanding of the true meaning of the myriad visits made to the student medical clinic. Yes, automatism can lead to indifference — and indifference can retard student medicine from emerging into the full role it should play in the scheme of medical affairs. True that many physical ills appear among the student body caused by infection and trauma — true, also, that many symptoms resulting from emotional problems can influence a student's scholastic accomplishment in the same or even greater degree than do physical ills. Nevertheless, the fact remains that enough serious illness occurs among students that the manner in which these illnesses and injuries are handled can determine the patient mortality rate in a student medical service. Similarly, enough severe and complex emotional ills occur in this age group to indicate that how they are handled can greatly affect the academic attrition rate and indeed the number of hostile, miserable people cast upon society for perhaps a lifetime of unproductivity.

There was a time when the medical profession looked with disapproval on the concept that student health services should accept and discharge clinical responsibility. However, with the passing of time and with the advent of voluntary health insurance plans, organized medicine has relaxed its feeling that campus physicians should preoccupy themselves with health education, public health, and preventive medicine.

Medical progress, public enlightenment, insight on the part of college administrators, and interest in student medicine as shown by the entry into the field of an increasing number of young well-trained physicians, nurses, social workers, nutritionists, and others has stimulated the current development of the science of student medicine to a degree unknown in prior times. We must be on guard, however, not to let complacency and laissez faire attitudes undermine this great opportunity. Weak discharge of responsibility, whether in the field of clinical practice, prevention of disease, or health education, can result in lost opportunity. Whether the laissez faire thinking appears as medical rules of thumb, obsolete lectures, routine sanitation orders, or a nurse assuming too much responsibility — all lead to automatism. In our emergence as an important academic and medical group, we must be alert to the penalties of the errors of our ways.

Just before the period of specialization started in this country, Osler recognized how vulnerable the highly respected family doctor was to conceit and self-complacency. In addressing the New York County Medical Society, he commented, "No class of men needs friction so much as physicians; no class gets less. The daily rounds of a busy practitioner tend to develop an egotism of a most intense kind, to which there is no antidote. The few setbacks are forgotten, the mistakes are often buried, and ten years of successful work tend to make a man touchy, dogmatic, intolerant of correction and abnormally self-centered. To this mental attitude the medical society is the best corrective and a man misuses a good part of his education who does not get knocked about a bit by his colleagues in discussions and criticisms." [2] I am sure if I were a student of the educational literature, an equally impressive warning from a master in that field of teaching could be found.

Let us not succumb to the temptations to which we humans are all too vulnerable. Instead let us discharge our obligation so thoroughly that praise, not criticism, will be our reward for effort. These latter warnings come from lessons learned in the 1953 survey which, for example, showed that in only 46 per cent of colleges, health service personnel attended off-campus professional meetings, and that in only 9 per cent of the health services did the staff hold regular meetings of its own. Another example is research. Of the 957 colleges having a health service of some kind, in only 160 or 17 per cent was research being conducted in the health service; and even more disappointing, in only 115 of these schools was the research concerned with student health problems. What we have been doing is applying the knowledge derived from others, but we cannot even continue to do that effectively without careful study of alternative methods. Never was there a time when health service directors as urgently needed a critical, unbiased examination of existing procedures and their effectiveness in relation to relative costs. I hope that in its report the committee on research will amplify this need. In essence, then, if student medicine *is* emerging as a respected campus specialty, having prestige with both academic and medical groups, it cannot long stay in that position unless we change our habits.

The 1953 survey again called attention to the myriad arrangements for medical care prevalent throughout the colleges and universities of our land. Circumstances are such that we cannot change the basic causes for the various arrange-

ments. We can, however, as an association decide on a common thread with which we can weave a formula of safety and protection for students in every college regardless of the arrangement. What other group in America knows better than we what these measures should be? Can we, as an association, much longer dodge our responsibility to American parents?

So much for lessons learned, some of which I am sure we have heeded; others we are thinking about, if not strictly addressing ourselves to these lessons.

Now for a word about the new role of student medicine as developed last year at the Fourth National Conference on Health in Colleges. As a worker on the survey committee, I was aware even before the discussion by the panel of presidents that administrators were hungry for knowledge of how to promote a good health service. Their special concern was frequently related to standards and the relationship of mental health to attrition. The number of personal letters from college presidents, particularly those of small colleges, appealing for information was quite revealing to the survey committee. The more administrators know and understand about health departments, the more they realize the advantage to them of a modern organization of this kind. A college president writing in the publication, *Student Medicine*, says of health services, "Its staff can furnish invaluable help to the administrator in determining minimum health standards for housing, including light, heat, and sanitary facilities. The staff can aid in food service inspection, in approving nutritious menus, in providing health examinations for food service employees, and in suggesting special diets.

"The service can call the attention of the administrative offices to unnecessary hazards which may exist on the campus in a hundred different phases of the operation of the physical plant. The staff can bring to many a faculty committee the breadth and wisdom of medical experience in the multiple phases of campus life. It can further help to bring understanding between campus and town, especially in the smaller university communities where 'town and gown' relations are often subject to recurring misunderstanding and recrimination.

"All of the valuable aid of a modern university health service, however, will not just happen. In the last analysis its potential can be fulfilled only if there is a recognition of its worth and a determination for its maximum use by the president of the university or college. He must see to it that adequate health funds, through fees, from endowments, or from part of the academic budget are made available to provide for the physical facilities and for an able staff. He must back the director of the health service in the policies needed for health care, and the administrator alone can integrate the service into the institution's life. An isolated service is of little value. To be sure, it will, even in isolation, take care of appendectomies and treat the sniffles. But its vitality will be measured by the extent to which it is in contact with both teachers and administrators, by the awareness on the part of the whole campus community of what the service can do, by the alertness of administrator in bringing the doctors and staff into consultation in the whole gamut of student affairs."[3]

Recently another university administrator in a discussion of budgets said to me, "I don't know how much longer I can sell a group of Wall Street bankers a large deficit for an academic year's expense, yet I feel the university I administer would suffer far greater in the long run with a balanced budget." After considerable more discussion of the pros and cons of balanced budgets versus deficits, I asked, "Didn't your institution raise tuition to the four figure level this year?" He answered, "Yes . . . and with it my institution takes on a moral obligation that parents do not waste tuition money on children who can't make the grade, regardless of the reason. I want to see my college hard to enter, but also I want to reasonably assure parents their boy or girl will stay in after admission."

After more conversation along the same line, the idea occurred to both of us that the student medical service has a large investigative and advisory responsibility in the area of selection. That aptitude performance has been the sine quo non of admission committees is no secret to this audience. However, has aptitude ever been carefully integrated with personality adjustment tests such as are conducted in the department of mental hygiene of the modern university health service?

We thus see that where awareness of the value of the psychiatric team was limited in the past to certain campus groups, such as some members of the medical or counseling staff and a few faculty members, presently administration senses the value of knowledge in this area to them, now that high tuition combined with high academic attrition places the institution in possibly an untenable competitive position. More and more the student medical service will be asked to contribute to the solution of this problem. I have often been told by colleagues when they were complaining about administration or rationaliz-

ing why more research was not conducted in their department, that so much time was taken up with patients that no time was left for research. I've always responded, "Of course, your staff needs some of the patient pressure removed. Have you approached your president with a well thought out proposal showing that data from the investigation you would like to sponsor could be helpful to him, too, and enlisting his help in financing the research? Probably he would help you defray the expense of extra manpower if you could demonstrate the leadership, know-how, and insight that would justify the expenditure."

Perhaps we ourselves have often been responsible, at least in part, for the administrator's indifference to our requests, because we have looked upon him more as father and ourselves as adolescents than as a colleague needing our help and advice.

Our present need for unification of records and the respectful treatment of them; the need to know the best alternative methods to further health standards, where direct health education is not possible and the college or university must depend upon indirect methods; the best alternative plans for financing the ever increasing costs of operating a health service; and the guarantee of survival of a medium of communication between departments all call for a high order of investigation and important consideration on the part of all of us.

Many more challenging ideas came forth from the Fourth National Conference on Health in Colleges. The panel which follows, I am sure, will carry on from here. Suffice it to say now, "Let us dedicate ourselves to the meeting of these challenges and remain emerged as a special group of medical and educational people with a special purpose within the framework of education."

In closing, let me remind you that last year your president, Dr. Dana Farnsworth, said that college health has come of age. If that be so, and I am sure it is, then this year let us face the responsibility of dealing with ourselves as young adults. Perhaps we have been children wandering in the wilderness and the voice we have heard we have been inclined to fear. Let us now accept the role for which we are destined and get along with our business as mature people.

We owe much to the individuals and committees which have made this meeting possible, our efficient secretary, Dr. Irvin Sander, the various committees whose chairmen will report this afternoon, and the numerous speakers we will hear. We are greatly indebted to Dr. Lewis Barbato and his committee on arrangements which not only made possible the program but the splendid setting too. To all of them go my sincere thanks and appreciation. To those of you who have been in this work longer than I goes my hope that you will speak both in this meeting and future meetings of your experiences. To you who are younger than some of us, please share with us your ideas, your hopes, and dreams for the career you plan in student medicine.

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Poison ivy dermatitis may be prevented by rubbing a lotion containing 4 per cent hydrous zirconium oxide into the skin within eight hours after contact with *Rhus toxicodendron*. G. A. Cronk, M.D., and D. E. Naumann, M.D., of Syracuse University, N. Y., find that the medicament alone or in combination with 1 per cent phenyltoloxamine dihydrogen citrate will not modify the course of established lesions, but both drugs singly or together are antipruritic.

G. A. Cronk and D. E. Naumann: Antibiotics & Chemother. 5:64-66, 1955.

Lancet CLINICAL REVIEWS

This department of THE JOURNAL-LANCET *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Disseminated Lupus Erythematosus with Massive Hemorrhagic Manifestations and Paraplegia

MAX H. WEIL, M.D.

Minneapolis, Minnesota

HEMORRHAGIC PHENOMENA may be an outstanding clinical feature in disseminated lupus erythematosus.[1] Bleeding complicates what so often already is a bizarre clinical picture, especially when it occurs in a hidden recess of the abdomen or the nervous system. It may be of considerable practical importance to suspect hidden hemorrhage so that hazardous surgery may be avoided. In the case to be reported, the abdominal findings suggested mesenteric artery thrombosis, perforation of a viscus, or other abdominal surgical emergency. Surgical exploration was delayed only because the patient was in a particularly precarious general condition. The cause of the "surgical" abdomen was massive retroperitoneal and subserosal hemorrhage, which was an unexpected necropsy finding. The presence of widespread internal hemorrhage, as part of the picture of acute disseminated lupus erythematosus, was not considered premortem.

CASE REPORT

The patient was an unmarried 24-year-old Negro waitress. Between 1933 and 1938, she was frequently treated in the pediatric clinics of the Cincinnati General Hospital for sore throats and upper respiratory infections. Tonsillectomy and adenoidectomy were performed in 1938 with prolonged postoperative bleeding. In 1946, the patient appeared in the clinic with an erythematous papular eruption over the left cheek and chin which improved with penicillin ointment. She had noted such face lesions yearly, usually in the fall, since the age of 6. In 1947, the patient had blepharitis, sinusitis, and alveolar abscesses and was treated with dental extractions and local and systemic sulfadiazine. In 1949, she exhibited evidence of mild pelvic inflammatory disease; cervical smears and cultures were negative for gonococci. During treatment of this illness with intramuscular penicillin, she complained of swollen, painful joints, edematous ankles, and chest pain.

In August 1950, the patient returned because of a carbuncle of the neck which was incised. She gave a history of intermittent migratory joint pains and morning stiffness of two and one-half years duration. Weight had decreased from 115 to 94 lb. in that period. She felt much better during her first pregnancy, but symptoms recurred three weeks after an uneventful delivery in July 1949. At the medical clinic, she was found to have a low-grade fever, fusiform swelling of the finger joints, a mitral systolic murmur, and generalized nontender lymph node enlargement. Urinalysis revealed a trace of albumin and 2+ glycosuria. The white blood count was 6,900. Rheumatoid arthritis was diagnosed. She was not seen again until September 1952 when reddish brown spots, which darkened when exposed to sunlight, were noted over the malar areas of her face. A glucose tolerance test was normal.

On February 3, 1953, the patient entered the hospital because of fever, chills, cough, and right-sided pleuritic pain of one day's duration. Three weeks earlier, bleeding ulcers had appeared on her gums and palate, followed by generalized muscle and joint aches. On physical examination, the patient was acutely ill, dyspneic, and pale with a temperature of 102° F. and blood pressure of 120/70. The periorbital tissues were puffy and hyperkeratotic pigmented maculas were distributed over the butterfly area of the face. Generalized firm, discrete lymphadenopathy was again noted. The gums were hy-

MAX H. WEIL, *a former intern at Cincinnati General Hospital, is now a research fellow in internal medicine at the University of Minnesota.*

From the Department of Medicine, College of Medicine, University of Cincinnati.

pertrophic and bleeding. Physical and roentgenographic findings indicated right upper lobe pneumonia. The hemoglobin was 7.7 gm. per cent; hematocrit 24 per cent; red blood count 2.46 million per cu. mm.; white blood count 6,900 with 90 per cent neutrophils; platelet count (direct method) 106,000. A sickle cell preparation was negative. Clotting and prothrombin intervals were normal. A bone marrow preparation for lupus erythematosus cells was positive. Urine contained 2+ albumin, up to 5 white and 2 red cells per high power field, and 3 granular casts. The blood urea nitrogen was 23 mg. per cent and phenol sulfonphthalein excretion was 60 per cent at two hours. The quantitative blood Kahn test was 120 units. The albumin/globulin ratio was 3/3. Sputum and blood cultures yielded alpha hemolytic streptococci. When penicillin and streptomycin were administered, improvement was rapid and she was afebrile in four days. One unit of packed red blood cells was administered. She left the hospital against advice on February 19, 1953. Disseminated lupus erythematosus was first diagnosed during this admission.

On March 2, 1953 the patient was readmitted because of sharp, deep, penetrating epigastric pain and vomiting of two days' duration. She had been obstipated for four days and was in great distress at the time of admission. Periorbital edema and a butterfly rash were again noted. The abdomen was slightly distended and prominent guarding and rebound tenderness were noted in the midepigastrium and left upper quadrant. Peristalsis was active. Percussion tenderness was found in the left flank.

Laboratory data were as follows: hemoglobin 12 gm. per cent; WBC 8,100 with 85 per cent neutrophils; urine, 3+ albumin and loaded with white blood cells, guiac positive. Vomitus and feces were both guiac positive. Blood amylase was 52 units (Bodansky). Blood nonprotein nitrogen was 54 mg. per cent. Escherichia coli were cultured from the urine. Serial liver profile studies revealed pronounced hepatocellular damage without bilirubin retention. Flat and erect roentgenography of the abdomen showed hepatosplenomegaly, ascites, and moderate paralytic ileus. Intravenous pyelography demonstrated prompt excretion of dye into the bladder, but the renal outlines were obscure.

Surgical exploration was advised for suspected mesenteric artery thrombosis. The patient was considered a poor surgical risk, however, and operation was delayed in the absence of localizing signs.

Streptomycin and penicillin were administered. During the evening of March 3, severe edema of the face and eyelids appeared, and maximum abdominal tenderness had shifted to the right upper quadrant. By the next day, maximum pain had shifted to the left of the umbilicus, retinal hemorrhages were observed in the right eye, and the WBC had increased to 10,050. An intravenous drip of 25 mg. ACTH daily had no noticeable effect. Gastric suction was instituted. By March 5, the patient had improved slightly. Maximum abdominal tenderness had returned to the right upper quadrant. Flatus was passed, but no stool. An abdominal fluid wave was elicited but paracentesis yielded no fluid.

On March 6, continuous hiccoughing, retching, and blood-tinged vomitus appeared. A barium enema showed irritability of the ascending colon; chest fluoroscopy revealed limited motion of the right diaphragm and a left-lower thoracic paravertebral mass. Admission blood culture grew alpha-hemolytic streptococci and Escherichia coli. Aureomycin therapy was accordingly added. During the course of the following two days, abdominal pain was intensified and the patient became more apprehensive. The white blood count had increased to 23,000 and the temperature was 101° F. On March 9, bladder distention became apparent and the patient was unable to move her legs. On the following day, she exhibited flaccid paralysis and loss of all sensory modalities below the seventh thoracic vertebra. Functional transection of the spinal cord was attributed to a metastatic abscess. Lumbar puncture was not advised because of suspected increase in intracranial pressure. Bleeding into the digital pads caused discoloration of the distal fingers. Blood cultures of March 7 and 8 had remained sterile. Blood pressure fell to 80/60 during the afternoon of March 10. Acute congestive heart failure followed and oxygen, aminophylline, lanatoside C (Cedilanid), and meperidine (Demerol) allowed transient improvement. The WBC had now risen to 61,000 with 99 per cent neutrophils; platelets 96,000; and blood urea nitrogen 39 mg. per cent. Ascending paraplegia caused increasing dyspnea. At 1 A.M. on May 11, she had mild convulsive movements of the left arm, became cyanotic, and died.

Necropsy was performed one hour after death. On incision of the skin, a large amount of clear fluid exuded from the subcutaneous tissues. Fresh adhesions bound the parietal pericardium to the anterior chest wall. The pericardial cavity was obliterated except for the space occupied by 30 cc. of thick, cloudy, pink-yellow fluid. One mitral leaflet was tightly adherent to the endocardium of the ventricle. Petechial hemorrhages were scattered over the endoeardium. A massive retroperitoneal hematoma occupied the proximal jejunal mesentery. This hematoma extended from the ligament of Treitz to the ileocecal valve. Subserosal hemorrhages involved the large and small bowel. A thin layer of subarachnoid blood covered the occipital cortex. Subdural clotted blood surrounded and compressed the spinal cord between T_4 and L_3.

Microscopically, the pathologic picture of disseminated lupus was well illustrated. There were "wire loop" lesions in the glomerular tufts, periarteriolar fibrosis in the spleen, acute epicarditis, and massive aggregations of hematoxylin bodies in the lymph nodes. The mitral valve was bound to the left ventricular wall by scar tissue, probably a healed Libman-Sacks lesion.

Fresh massive hemorrhage was noted in sections of the mesentery and intestine. The spinal cord was necrotic in the area of hemorrhage with minimum surrounding inflammatory reaction. Terminal septicemia and pyemia were reflected in suppurative foci in several mesenteric lymph nodes, the presence of cocci in miliary pyemic lesions of the heart, and pancellulitis of the bladder wall. Two small muscular-type arteries, one in the colon and the other in the mesentery, presented early necrotizing angiitis of the type seen in periarteritis nodosa.

COMMENT

Hemorrhagic manifestations may dwarf other findings in disseminated lupus erythematosus. Thrombocytopenia is a common laboratory finding and was found in approximately one-half of Michael's reported series of 111 patients. Pronounced platelet deficiency with a clinical picture resembling thrombocytopenic purpura has been successfully treated with splenectomy.[2] Inflammatory and fibrinoid changes in the wall of blood vessels, such as were observed in the present case, may also be responsible for focal hemorrhage.[3] Moreover, Conley and Hartmann dem-

onstrated a circulating anticoagulant in two disseminated lupus patients who displayed hemorrhagic phenomena.[4] Frick studied 2 additional patients with prolonged clotting time and circulating anticoagulant at the University of Minnesota hospitals.[5] In the light of present knowledge, hemorrhagic manifestations in this disease are accordingly traced to platelet deficiency, necrotizing angiitis, circulating endogenous anticoagulant, or to a combination of these conditions.

In the reported case, only a minimum reduction of the platelet count occurred so that thrombocytopenia was not a cause of hemorrhage. Angiitis was of mild degree and, in the absence of hypertension, it is doubtful that arterial rupture occurred on this basis. Sepsis was a prominent feature of the patient's terminal cause. While the role of toxemia cannot be discounted, septic angiitis was unlikely as no abscesses were related to the areas of major hemorrhage. Finally, in the absence of further blood coagulation studies, the appealing postulation that an endogenous anticoagulant was involved remains conjectural.

SUMMARY AND CONCLUSIONS

A case of disseminated lupus erythematosus is reviewed in which the clinical history and autopsy findings supply an almost classic description of this disease. In addition, the clinical examination suggested an acute, "surgical" abdomen. Paraplegia subsequently developed two days before death. Massive retroperitoneal and intraspinal hemorrhage was found unexpectedly at necropsy.

The nature of the hemorrhagic disorder in this disease is commented upon. It is of practical importance to consider bizarre manifestations in disseminated lupus erythematosus as arising from hidden hemorrhage. These symptoms may mimic acute surgical conditions.

Permission to review case material in the department of pathology of Cincinnati General Hospital, and the aid of Dr. Pearl M. Zeek, Associate Professor, in its interpretation are gratefully acknowledged.

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Progressive, bilateral hydronephrosis may be a manifestation of systemic sarcoidosis. C. C. Pearson, M.D., and J. Tate Mason, M.D., of the Mason Clinic, Seattle, report that epitheliod-cell granulomas with fibrotic and cystic areas were found by biopsy in a man with bilateral hydronephrosis and ureterovesicular obstruction. After treatment with cortisone, 100 mg. in forty-eight hours initially and then 25 mg. twice a day for three weeks, the patient has remained free of symptoms, and pyelographic evidence of the distention is not demonstrable.

C. C. Pearson and J. Tate Mason: Bull. Mason Clin. 9:16-23, 1955.

The following letter from Dr. Ancel Keys, head of the department of physiological hygiene at the University of Minnesota, to Dr. J. A. Myers and the readers of The Journal-Lancet, *was delayed many months en route from Europe. Since Dr. Keys' letters always hold so much of interest to our readers, we are glad of the opportunity to present it even though it bears the date of many months ago and Dr. Keys is now home again in Minnesota.*

Notes from a Medical Journey

November 2, 1954
Geneva, Switzerland

Dear Jay:

The final report of our Joint FAO/WHO Expert Committee on Nutrition has just been approved and the result, an untidy mass of mimeographed pages, litters the desk. At this stage, as always in such matters, it seems improbable that the outcome of so much debate, mental sweat, and compromise can really be of use to anyone. Obviously paragraph 3, section C, is sheer nonsense, paragraph 2-5, section E, are unintelligible to me, and the whole of section B carefully dodges all the important issues. Perhaps it will all look much better when it gets into print after Dr. Wallace Aykroyd has polished the English and I, like the rest of the committee, have recovered from the post-drafting letdown after seventy hours of unremitting work.

Anyway, it is a relief to look out across the blue reflecting lake to the ridge on ridge of snow-clad mountains ending in Mont Blanc, that sharpest white merging in the distant clouds. Outside the window the autumn leaves are flying and the fall colors, so brilliant a week ago, are fading, though the park of the Palias des Nations below me is still a glory of flower beds and the rich yellows and reds of trees rising from a sea of green lawns. The brightest spot of all is the semicircle of the flags of all the member nations. I spot the stars and stripes, of course, and each of my colleagues picks out his own symbol in the array.

In a few hours we separate -- Rao to Bombay, Bengoa to Venezuela, Terroine to Paris, Darby to Basutoland, Salcedo to Manila, Stiebeling to Washington, Aykroyd to Rome, Platt to England and then to the Gambia, Wright to England, Scrimshaw to Guatemala, Dols to the Hague, and I back to Minnesota. Perhaps we can carry with us some measure of new knowledge, new understanding, new tolerance and we may even hope to impart some of this to our colleagues at home. There is little or no politics in these expert meetings. As long as we stick to concrete questions of nutrition and health, as long as we worry about scientific knowledge and its proper application, we forget about national jealousies, fears, and military aspirations. And we discover how much we can learn from one another.

The committee went on record urging the need for research on the influence of nutrition on the development of coronary and other degenerative

diseases and the value of international epidemiological studies of the experiments of nature as represented in different countries. This, of course, was my meat and I was able to make good use of the example of the World Congress on Cardiology, last September in Washington, where the opening session, organized by Paul D. White and myself, was devoted to this subject and proved to be a huge success. One of the most promising developments here in Geneva was the evidence of awakening of interest of the World Health Organization as shown by the discussions with me about forming a study group to advise WHO what they might appropriately do in this field. I contend that while WHO must give major attention to the job of helping the underdeveloped countries in elementary matters of public health and medical education, the more direct problems of the other countries cannot be totally neglected indefinitely without danger of losing their support. And the biggest of these problems which beset the United States as well as most of the other advanced countries are those of the chronic and degenerative diseases of metabolic origin. Outstanding in this group is coronary heart disease and the most intriguing and hopeful question is why this is so common in some countries and comparatively rare in men of equal age in others. International collaboration in research on this question is essential and the sponsorship of WHO in this problem would be of great moral if not financial aid.

Anyway, at my suggestion WHO has appointed Dr. Arrigo Poppi of Bologna, Italy, as a short-time consultant to spy out the land in this matter and he will shortly make a quick tour around Europe to assemble the opinions of leading cardiologists and public health experts on the atherosclerosis question as a field for WHO. It seems probable that a group of us will be called to Geneva next year as a study group to get more definitely at grips with the problem. The nutrition aspect will be in the fore because it is no longer possible to deny that the diet, particularly its fat content, has much to do with the development of athero and the subsequent coronary heart disease. It is good to see the growing recognition of the significance of our own work on this in Italy, Spain, and England as well as at home. Perhaps the enthusiasm about all this I expressed in my letters to you during the last couple of years was not misplaced after all.

On my way to Geneva I managed to have conferences in Rome and Bologna, as I think I wrote you, and further correspondence along the way make it pretty certain that we shall again be off on field work in February of 1955. We must get more data on the blood picture of Italians living at different levels of fat in the diet, we want to check, personally, the story of the South African Bantu who is reported to be remarkably free from coronary occlusions and who lives on a very low-fat diet, of corn meal, and above all we want to put our method of separating the blood plasma lipoproteins by paper electrophoresis to work on some of these populations.

In Minnesota at least, we now can separate the alpha from the beta lipoproteins in 0.1 cc. of serum on a strip of filter paper moistened with buffer solution with a potential of 185 volts between the two ends applied for 15 hours in a moist chamber, cut the paper between the separated portions, and extract and measure the cholesterol in each portion. Our method has been developed from that of Bengt Swahn, who worked with us last year

in Italy, and is rather similar to a method recently described by Nikkila in Finland. Unlike the other methods of this type, we have taken the trouble to run hundreds of duplicates and to check it by parallel measurements with the method of the late E. J. Cohn in which the various proteins are separated by precipitation by alcohol at minus 5° C. It looks good and has the advantage that it can be done readily, we think! in the field where we may have only primitive laboratory facilities. While I am here in Europe, Dr. J. T. Anderson and others in the Lab. back home are busily engaged in applying both this and the cold alcohol method to the members of the Minneapolis Fire Department and to the coronary patients being rounded up by Dr. Reuben Berman. And my former student, Dr. Flaminio Fidanza is trying it out in Naples.

The point of the fuss over the beta lipoprotein measurement is that it may be even more closely related to the development of atherosclerosis than the total cholesterol. Of course the difference cannot be very great because beta lipoprotein is almost half cholesterol and most of the total cholesterol of the serum is in this fraction. From our preliminary work, in trying to distinguish between patients with coronary disease and healthy controls, the beta lipoprotein cholesterol seems to be a trifle better than the total cholesterol and both of these measurements prove to be better, in our hands, than Gofman's "Sf" analysis with the ultracentrifuge. We still think that none of these methods is much good in attempting to predict the coronary future of the individual patient but they are all certainly valuable in research with groups. Incidentally, Gofman's new "atherogenic index" seems to be nothing but a complicated and very expensive way of estimating the cholesterol in the beta lipoprotein fraction in the serum, or, at least, that is about what it adds up to.

But now I must pack and face the prospect of no sleep for the better part of forty-eight hours while I hurry home, changing 'planes in London and Boston with a hectic stopover at the Massachusetts General Hospital meeting of the Research Committee of the American Heart Association. There we shall have to select among some 100 applicants for Heart Fellowships to keep our commitment for next year to around $350,000 in this category. Phooey! to those who think this traveling around is an easy life.

Probably my fatigue and somewhat ill-humor at the moment is heightened by the fact I seem to have picked up a flu "bug" from Guatemala via my friend Dr. Nevin Scrimshaw. I feel far from right, and I have just stopped to check my temperature and find it is 102°. Damn!

Anyway, I am anxious to get home and trust that aspirin and phenobarbital will waft me over to England and across the Atlantic. I hate airplanes but they do wonders in keeping an 11,000-mile itinerary within possible time bounds. By the time I am back in Minnesota, you will still be settling election bets.

With all the best until then to you and our good friends in Minnesota,

As ever,

Ancel Keys

Legg-Calvé-Perthes Syndrome, by Charles Weer Goff, 1954. Springfield, Illinois: Charles C Thomas. $10.75.

The osteochondroses epitomized by Legg-Calvé-Perthes disease are subjects of great interest to orthopedists, pediatricians, roentgenologists, and appear in the practice of the general physician where they frequently cause difficulty as far as differential diagnosis is concerned. For this reason, a book limited to the thorough discussion of these conditions is an extremely valuable addition to the physician's library. It is unfortunate that this monograph is not ideally fitted as a reference book on these conditions.

The author has reviewed the literature extensively and has had much experience in the treatment of these conditions in his own practice. His discussion of the subject, however, is very poorly organized and his conclusions seem to be colored by his own personal opinions and prejudices. For instance, on the basis of the treatment of 10 patients with small doses of Aureomycin continued over prolonged periods of time, he is willing to advocate this type of treatment as a valuable addition to the regimen of treatment which consists otherwise of methods of preventing the patients from bearing weight on the affected hip until healing has occurred.

The author attempts to establish a body syndrome which occurs in association with Legg-Calvé-Perthes disease. This syndrome is poorly defined and it is doubtful whether it actually exists. If the material were better organized, the views of the author might be a little clearer.

Leonard F. Peltier, M.D.

•

The Encyclopedia of Child Care and Guidance, edited by Sidonie M. Gruenberg, 1954. 1,016 pages. $7.50.

This book, by a leader in America in the study of children, can be of tremendous help to mothers. It contains an enormous amount of information arranged in alphabetical order. I was impressed by the sanity of the many articles.

There are more than 1,000 pages filled with wise answers to the many questions that may plague a mother as her child begins to grow up. The book can serve as a guide not only to parents but to teachers, social workers, physicians, nurses, clergymen, group workers, youth leaders, camp directors, and all those who work with children.

Walter C. Alvarez, M.D.

BOOK REVIEWS

The Auxiliary Heart, by William Walter Wasson, 1954. Springfield, Illinois: Charles C Thomas. 184 pages. $10.50.

This book is concerned primarily with the lesser circulation. Chapters include anatomy, physiology, and diseases of the chest. The title emphasizes the essential accessory role in the pulmonary circulation that is played by the resilient muscular walls of the smaller blood vessels.

The book is written by an experienced radiologist. The proportion of x-ray pictures included in the many illustrations bears witness to this fact. Many of the pictures are good.

The compilation of references and the appended historic review are noteworthy. The impression that many books have been written about the chest and the pulmonary circulation is confirmed.

Victor A. Gilbertsen, M.D.

•

Depression, edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D., 1954. New York City: Grune and Stratton. 277 pages. $5.50.

In the foreword, the editors say that the most outstanding problems of psychopathology today are anxiety and depression. Since the problem of anxiety was covered in an excellent symposium several years ago, the next logical step was to publish a symposium on depression.

The symposium on depression consists of 16 chapters written by 24 eminent members of the American Psychopathological Association. The general practitioner should find the following chapters especially interesting and helpful: "Clinical Diagnosis of Manic-Depressive Psychosis," "Children's Reactions to the Death of a Parent," "Reactive Depressions in Later Life," "Some Problems in Electric Convulsive Therapy of Depressions," "The Hospital Treatment of Involutional Psychoses," "The Influence of Physical Treatment Methods in Mental Disease Upon the Defensive Operations of the Ego," "The Treatment of Various Types of Depression in a General Hospital," and "Acute Depressive Reactions to Surgical Treatment for Cancer." By naming the above 8 chapters, I do not mean to imply that the other chapters are not equally as valuable; they would be, perhaps, of more interest to the physician anxious to know more about the complicated problem of depression.

Spaced in between every third to fifth chapter is a discussion of the previous chapters which will also be of real value to the reader. A number of case histories are included in the various chapters.

In conclusion, I believe that this symposium on depression represents a real contribution to the problem of depression, and should be on the shelf of every physician who is interested in this subject.

John W. Schumacher, M.D.

•

Clinical Approach to Jaundice, by Leon Schiff, M.D., 1954. Springfield, Illinois: Charles C Thomas. $3.75.

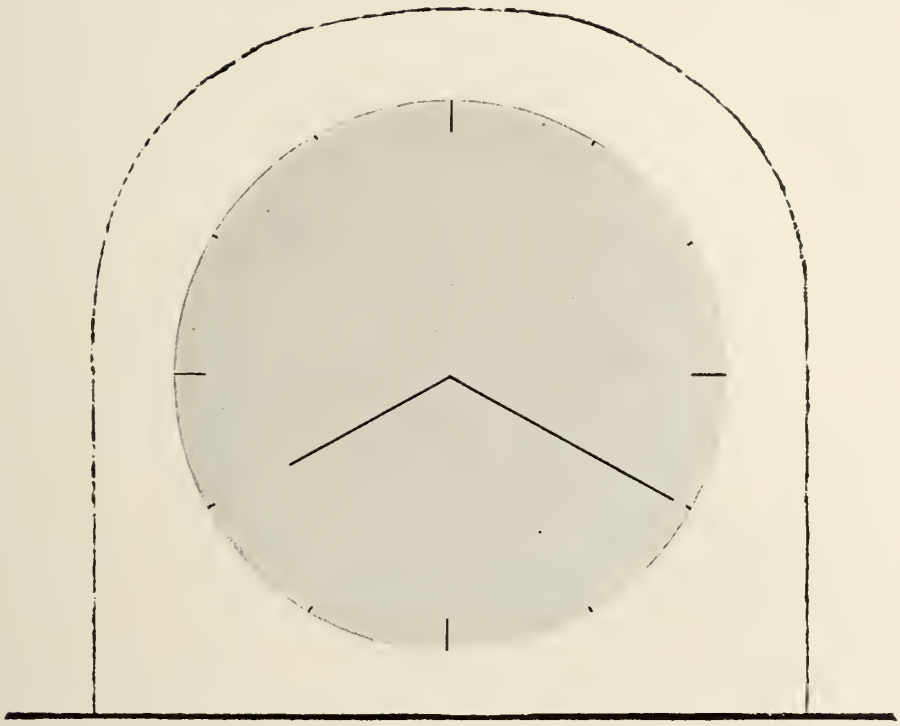
In this excellent monograph on jaundice, the author, who is well versed in the pertinent laboratory procedures, places emphasis upon the clinical approach. Indeed, it is the analysis of such tests which makes this article valuable for the practicing phsyician, internist, and surgeon alike.

The discussion of the liver function tests is directed toward the better recognition of various types of jaundice including hemolytic neoplastic calculous and parenchymal types as well as hepatitis and cirrhosis. The roentgen examination is discussed in view of its limited value in the differential diagnosis of jaundice.

In the experience of the author and associates, needle biopsy of the liver has given valuable information in distinguishing hepatocellular from obstructive jaundice and particularly in establishing the presence of hepatitis and cirrhosis. The skills in doing liver biopsy may not be as readily available for smaller groups, and, by and large, biopsy is not commonly pursued. In the author's series of 1,075 cases, no deaths were attributable to biopsy, although severe hemorrhage occurred three times.

An adequate bibliography is included and the number of references to the articles of Dr. C. J. Watson, of the University of Minnesota, attest to his leadership in the investigation of liver disease.

C. A. McKinlay, M.D.



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Green, M.A.: Ann. Allergy *12*:273

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American College Health Association . . .

Notification of the death of Dr. Henry G. Poncher, director of health service, Valparaiso University, Valparaiso, Indiana, on May 31, 1955, has reached this office from Dr. L. M. Dyke, University of Illinois, secretary-treasurer of the Illinois section. Dr. Poncher was a professor of pediatrics and head of that department at the University of Illinois College of Medicine prior to his entry into the field of college health work.

° ° ° °

Samuel E. Leard, M.D., Director of the Division of Student Health at Boston University is the co-author of the book, "Prolonged and Obscure Fever" with C. S. Keefer, M.D. Publishers are Little, Brown and Company, Boston.

° ° ° °

Miss Mittie Smith, R.N., is thought by Dr. A. O. DeWeese, director of health service at Kent State University, Kent, Ohio, to hold the record in length of service as a resident nurse. Miss Smith entered the Kent State University Health Service in 1921 and retired this year. For thirty-three years her only home was her quarters in the health service and her social life and interest were the campus activities. As the children of former students became students, she administered to them and in some instances to their grandchildren.

° ° ° °

Dr. DeWeese also writes to praise the placement service of the ACHA. Dr. George A. Prochnow, recently appointed chief of the clinical staff at Kent State University was first approached as a result of his listing with this office.

D. C. Reynolds, M.D., director of student health service at Oregon State College in Corvallis, Oregon wants a full-time physician on a ten-months' employment basis beginning September 1, 1955. He must be a graduate of a Grade A medical school with an Oregon license or eligible for reciprocity with Oregon. If interested, write to Dr. Reynolds at Oregon State College.

° ° ° °

Ray E. Andrews, M.D., has notified this office that he has accepted a position in student health work at Lehigh University in Bethlehem, Pennsylvania.

° ° ° °

Dr. Nestor M. Santiago, staff physician at the University of the Philippines Health Service, Quezon City, Philippine Islands, has spent the past year at the Harvard University School of Public Health. He received his Master of Public Health degree in June. During the last two weeks of June, Dr. Santiago made a brief tour of central and eastern United States to visit a number of health services. We do not have his complete itinerary, but he spent some time at the University of Minnesota, the University of Michigan, Wayne University, Harvard University, and several others. He sailed from New York on July 5 to return to the Philippines by way of Europe and the Middle East.

° ° ° °

Dr. Warren E. Forsythe, recently retired as director of the student health service at the University of Michigan after thirty-eight years, has presented several old publications to the ACHA. Two of them are, "A Report of Twenty Years Experience in the Department of Phys-

(Continued on page 34A)

taste is as important to the young patient as effectiveness is to you. In antibacterial therapy Gantrisin (acetyl) Pediatric Suspension is useful on both counts because of its delicious raspberry flavor without "medicine" aftertaste, its wide antibacterial spectrum and notable freedom from gastro-intestinal upsets and other side effects.

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(Continued from page 32A)

ical Education and Hygiene in Amherst College," dated June 27, 1881, and "The Twenty-fifth Annual Report of the Professor of Physical Education and Hygiene to the Board of Trustees of Amherst College," dated June 29, 1886. These publications will be kept in the archives of the association by the secretary.

News Briefs . . .

North Dakota

A CLINIC is scheduled for construction in Rolla next spring. Dr. E. H. Goodman is actively engaged in planning the new building and has already purchased a lot on which it will be erected.

* * * *

DR. ROBERT E. LUCY, of the DuPuy-Sorkness Clinic, Jamestown, has been elected a fellow-elect of the American Academy of Obstetrics and Gynecology.

* * * *

DR. ERIC W. WALTER, of the Quain and Ramstad Clinic at Bismarck, has been certified by the American Board of Radiology. This certification qualifies Dr. Walter for examination and specialty of diseases by x-ray, radium, and radio isotopes.

* * * *

DR. DOUGLAS T. LINDSAY has resumed practice in the department of orthopedic surgery at the Fargo Clinic after serving in the Army for two years. Dr. Lindsay is a former director of the North Dakota Crippled Children's Services.

DR. BAGHER SOTEEDEH has become associated with Dr. John J. Ayash, eye, ear, nose, and throat specialist in Minot. Dr. Soteedeh practiced at the Lovelace Clinic in New Mexico for the past year and, prior to that time, spent several years in postgraduate study in New York City. He is a diplomate of the America Board of Otolaryngology and the American Board of Ophthalmology.

* * * *

DR. EDWIN O. HIEB, of the DePuy-Sorkness Clinic at Jamestown, has been granted a leave of absence to take a residency in internal medicine at the University of Minnesota Graduate School. Upon completion of his course, Dr. Hieb will resume his association with the clinic.

* * * *

DR. MATT PLATTEN, of Cleveland, Ohio, has joined the staff of the Tioga Clinic at Williston. Dr. Platten replaces Dr. R. P. Froeschle who recently left the clinic. He is a graduate of Ohio State University School of Medicine.

* * * *

DR. A. MARTENS, recently of Kildeer, has established practice in Bowman with an office in the Tri-State Clinic. Dr. Martens received his M.D. from the University of Lwow in Poland in 1934, and practiced medicine and surgery there for several years.

Minnesota

DR. WILLIAM H. FELDMAN, of the Mayo foundation, was awarded the annual Trudeau medal by the National Tuberculosis Association. Dr. Feldman's careful studies of the action of drugs on tuberculosis contributed immeasurably to the successful use of chemotherapy in tuberculosis. The award is one of the highest presented by the association.

* * * *

DR. OWEN H. WANGENSTEEN, head of the department of

(Continued on page 38A)

The Journal Lancet
SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

Chondromalacia of the Patella

DAVID B. HORNER, M.D.
Minot, North Dakota

Arthrotomies of the knee for various internal derangements have brought an interesting lesion to the attention of American investigators. This entity, characterized by degeneration of a circumscribed portion of the articular face of the patella, was termed "chondromalacia of the patella" by Konig as far back as 1924.

Since then, numerous reports have appeared in the European literature concerning this condition, but until recently only a few scattered articles have been contributed by American investigators. This dearth of reports is particularly strange in view of the fact that the disease occurs frequently and produces severe and persistent symptoms.

ETIOLOGY

Despite the fact that degenerative changes have been described in the articular cartilage of the patella for many years, opinion differs concerning the cause of this condition. Its similarity to degenerative arthritis was recognized early by such workers as Lawen[1] and Konig.[2]

Trauma as a cause was advanced primarily by Aleman,[3] who explained mild cases in which a specific history of trauma could not be obtained, on the grounds that minor injuries could produce minute fractures sufficient to cause onset of the condition. Subsequent review of a portion of his work and additional studies by Karlson have thrown considerable doubt on this author's contention.

Later work carried out by such individuals as Bennett and associates[4] showed that degenerative changes in the articular surface of the patella occurred in all individuals after the second decade without a history of specific trauma.

Thus, our present concept is that degeneration of the patellar cartilage can occur either as a result of or without specific onset of trauma.

In an excellent monograph, Hirsch reported the conditions which can cause cartilage breakdown. He observed that pressure is essential for cartilage nutrition, but that, if pressure is increased for too long a period of time or repeated too often, degenerative changes result. The resultant damage produces loss of elasticity which is followed by fissure production.

PATHOLOGY

The earliest degenerative changes are uniformly noted on the medial aspect of the patella with the entire surface ultimately involved in severely advanced cases.

The studies by Wiberg[5] indicate that in moderate flexion of 20 to 50 degrees, the area of lateral articular cartilage makes direct contact with the femoral condyle, with the greatest stress present against the central ridge. As flexion in-

DAVID B. HORNER, *a 1944 graduate of New York Medical College, is attending orthopedic surgeon at Veterans Administration Hospital and on the staff of Trinity and St. Joseph's Hospitals and the Northwest Clinic, all in Minot, North Dakota.*

From the department of orthopedic surgery, Northwest Clinic, Minot, North Dakota.

creases, this pressure against the central longitudinal ridge diminishes until at 90 degrees it is completely gone. During flexion, the lateral patellar facet fits smoothly against the lateral femoral condyle, while the medial facet of the patella presents a convex surface to a convex femoral condyle from 90 degrees of flexion onward.

A summary of the gross and microscopic findings has been thoroughly presented in a review by Bronitsky.[6] In the early stages, the shiny translucent appearance of the cartilage is lost and replaced by areas that are opaque and tan to yellow in color. This area is considerably softer in consistency. Fissures appear as degeneration becomes more pronounced and the cartilage is gradually broken down with the exposure of subchondral bone. In severe cases, the entire articular surface may be exposed with the bone beneath it sclerotic and eburnated.

Microscopically the cartilage shows fibrillation, loss of cells, and abnormal staining reaction with the thickness of the cartilage reduced. The subchondral bone is normal until exposed and then proliferative fibrous changes are seen.

SYMPTOMATOLOGY

The diagnosis is often obscured because the patient has difficulty in localizing and describing the type of deep-seated pain. Usually the history is that of chronic knee discomfort of variable severity. This pain is often accompanied by a tendency for the knee to give way. Frequently a transient locking or ratchet-like movement of the knee occurs which results in loss of full motion and occasional joint swelling.

Objectively, joint motion produces crepitation. Subpatellar crepitus can be elicited by grasping the patella firmly and grinding it against the underlying femoral condyles. This motion usually elicits pain. Thickening and swelling of the knee may be noted. Also, if symptoms are chronic enough, quadriceps muscle atrophy of a variable degree is present.

Roentgenographic studies of the patella are usually negative, especially in early cases. Occasionally, tangential views of this structure show small osseous chips present along its articular surface. Notching of its central portion may be noted, but its significance is questioned by some authors. Pneumography has had limited value in the author's experience. According to Soto-Hall[7] the diagnosis rests on a combination of the following signs and symptoms: (1) subpatellar crepitation on active movement, (2) variable deep-seated pain in the knee, (3) tenderness on percussion of the patella, (4) pseudolocking or ratchet rhythm, (5) a subjective feeling of instability, and (6) occasional recurrent subluxation of the patella.

TREATMENT

In early cases, rest in the acute phase is achieved by means of a plaster cylinder cast for three weeks. This is followed by active quadriceps exercises under the guidance of a physiotherapist and ultimate use of weights and recovery

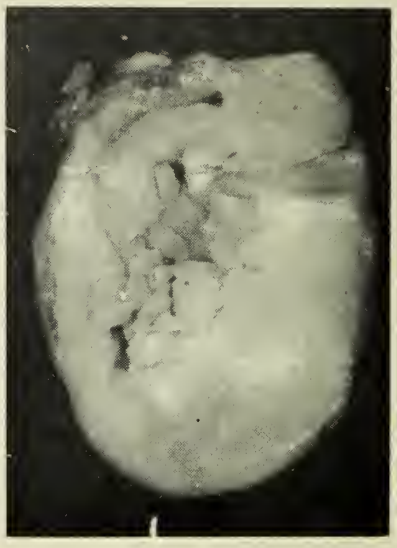

Fig. 1. Fissuring and softening of the patella in a 24-year-old school teacher with a history of chronic, deep-seated pain in the joint. Prompt recovery of function postoperatively.

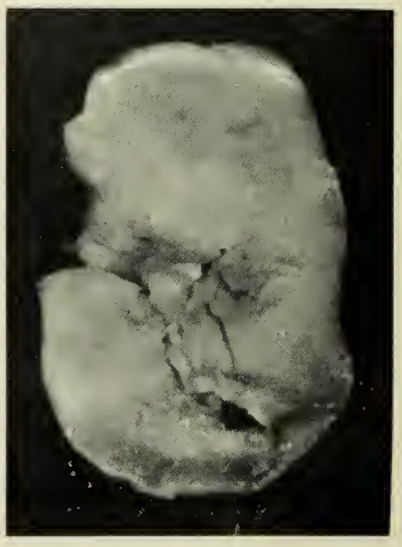

Fig. 2. Pronounced destructive change in the patella of a 28-year-old farmer who had been struck in the right knee one year before by a cow. Joint swollen, motion limited. Function fully restored six weeks after total chondrectomy.

Fig. 3. Central destruction of area of patellar cartilage in a 37-year-old housewife who fell three months prior to surgery. Chronic dull aching pain in knee with inability to climb stairs or kneel. Postoperative recovery excellent after total chondrectomy.

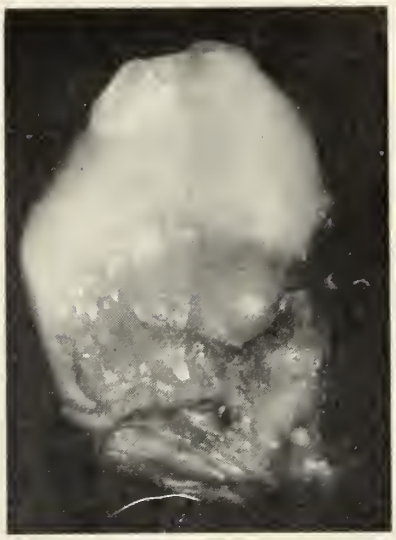

Fig. 4. A 15-year-old boy fell on his knee in a ball game five months prior to surgery, injuring patella. Chronic swelling of knee with periodic incomplete locking of knee and a frequent tendency to give way. Full recovery of knee function three weeks postoperatively.

of full power. If the symptoms are disabling or persist, surgical intervention is indicated (figures 1, 2, 3, and 4).

Upon exploration of the knee joint the following procedures are carried out as indicated:

1. Chondrectomy. If the changes are limited and localized, the fissured and deformed cartilage is trimmed and smoothed out by sharp dissection with a scalpel blade.

2. Total resection of the articular surface. This is particularly suited for adolescents and young adults without advanced traumatic changes in the joint but in whom more extensive destruction of the articular surface of the cartilage is present. In such cases, dissection is carried out by means of a sharp, broad osteotome and the cartilage is removed cleanly to healthy subchondral bone. The joint is thoroughly irrigated to remove any small fragments of cartilage. A search is made for any loose cartilage or osseous bodies. Any associated injuries to the menisci are dealt with in the usual manner.

3. Patellectomy is the procedure of choice in severe advanced cases, especially in older groups.

In all, postoperative care consists of early, intensive quadriceps exercises, initiated as soon as possible in the form of quadriceps setting exercises and followed by intensive quadriceps rehabilitation.

SUMMARY

Chondromalacia of the patella is a frequently encountered chronic disability of the knee joint. The condition occurs most often in young, otherwise healthy individuals with resultant, severe productive changes in joint function. Early treatment and rehabilitation offer the best prognosis for restoration of joint function, although some doubt is expressed as to whether further degenerative changes in the joint can be prevented.

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A Hazard of Hypertensive Drug Therapy

MICHAEL F. KOSZALKA, M.D., and
H. CHARLES WALKER, M.D.

Fargo, North Dakota

In recent years a variety of drugs have been made available for general prescription which are capable of producing pronounced reduction of blood pressure in hypertensive patients. At the beginning of this era, which was marked by the return to medical treatment of severe hypertension, a report to the Council on Pharmacy and Chemistry by Grimson and associates[1] warned that promiscuous use of these potent adrenolytic, sympatholytic, and ganglionic blocking drugs might be dangerous. In this short span of five years, several promising and widely used hypertensive agents have had to be abandoned because of immediate or delayed toxic effects. Well documented case reports of fatalities have been recorded.[2-4] All the drugs remaining in our present medical armamentarium that are capable of satisfactorily altering a fixed hypertensive have a relatively narrow range between therapeutic and toxic dosage. At times, the varying and often unpredictable hypotensive response to these agents, particularly those administered orally, may hasten rather than retard some of the natural consequences of the disease.

Until recently hexamethonium was the most satisfactory single antihypertensive agent. In recent months, a new related ganglionic blocking agent has been made available for general use which will undoubtedly replace hexamethonium. Pentolinium tartrate (Ansolysen) according to preliminary reports is approximately 5 times as potent as hexamethonium. Its action is more predictable, more prolonged, and it produces a better tolerated hypotension. Furthermore, this drug is effective orally in most patients.

On an accepted medical regime, a patient of ours developed an acute myocardial infarction which we believe was a side effect of Ansolysen therapy. Our purpose is to report such a complication and emphasize as a potential hazard any drug that drastically induces absolute or relative hypotension.

MICHAEL F. KOSZALKA, *a 1938 graduate of Georgetown University School of Medicine, is chief of medical service at Veterans Administration Hospital, Fargo, North Dakota.* H. CHARLES WALKER *is also affiliated with Veterans Administration Hospital, Fargo.*

REPORT OF A CASE

E. H., a 41-year-old white male, was admitted to the hospital November 22, 1954 with a history of headaches and dizzy spells of six months' duration and high blood pressure since 1944. The symptoms were of sufficient severity to interfere with his livelihood and daily comfort. Mild exertional dyspnea was his only other complaint. Past history was not contributory. Except for the presence of a blood pressure of 210 mm. Hg systolic and 110 mm. Hg diastolic in both standing and supine positions, his physical examination was negative. Serology was negative. Complete blood count was normal. Fasting blood sugar measured 81-mg. per cent. A 3+ albuminuria was present initially. A second urinalysis was normal. Blood urea nitrogen was 18-mg. per cent. Basal metabolic rate recorded −17 per cent. Urine specific gravity ranged from 1.002 to 1.022. Urea clearance was 95 per cent of normal. A 35 per cent phenolsulfonphthalein excretion was detected in the urine in one hour. A radiographic chest examination and an intravenous pyelogram were normal. A left ventricular hypertrophy pattern was present electrocardiographically (figure 1).

When the patient failed to improve after a week of hospital rest, therapy was initiated with reserpine (Serpasil) 0.25 mg. three times a day. One week later Ansolysen therapy was added beginning with 40 mg. twice a day before meals. The drug was increased by 20 mg. every three days as indicated. Blood pressure determinations were made with the patient in supine and erect positions. His standing blood pressure remained at a level averaging 180 to 200 systolic and 96 to 100 diastolic until December 28, 1954, when it was recorded at 142/92. At this time he was taking 160 mg. of Ansolysen twice daily. He began having mild episodes of effort angina usually between 6 and 9 P.M. which were relieved by rest or nitroglycerin so that no further increase was made, although higher blood pressure readings were being obtained. It was felt that he could be discharged safely into the care of his home physician and that the angina would clear up with adjustment to the drug. At no time was a standing systolic blood pressure of 120 mm. Hg or less recorded.

On the following day, severe chest pain was incurred shortly after an evening meal of average size. He was watching television at the onset. No history of alcoholic consumption or constipation was elicited. The pain was oppressive in character and radiated down into the left arm. It continued for one hour in spite of 4 sublingual nitroglycerin tablets, gr. 1/100, and did not subside until relieved by an injection of morphine sulfate and papav-

From the Medical Service, Veterans Administration Hospital, Fargo, North Dakota.

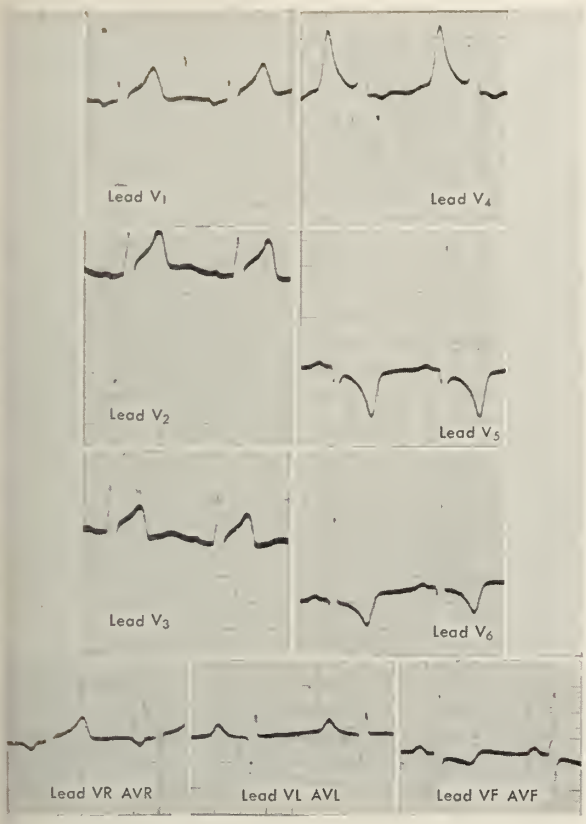

Fig. 1. Electrocardiographic tracing taken before therapy showing a left ventricular hypertrophy pattern.

erine hydroehloride. An electrocardiogram procured at the local hospital confirmed the diagnosis of myocardial infarction. At the suggestion of one of the authors, M.F.K., his personal physician gradually reduced the Ansolysen to 40 mg. twice a day and continued the Serpasil as previously. An average daily blood pressure of 150/90 was reported subsequently. He returned to our hospital for follow-up examination on January 19, 1955. A comparison of electrocardiographic tracings showed a superimposed pattern of anterior wall myocardial infarction (figure 2). When he demonstrated tolerance to graduated ambulatory activities, he was discharged again into the care of his physician. Continuation with 0.25 mg. of Serpasil three times a day and 40 mg. of Ansolysen twice a day was advised. Since the occurrence of this untoward complication, our patient henceforth was cautioned to take the medication with his meals to permit slower and more even absorption and avoid an exaggerated response. On his last follow-up on March 21, 1955, he remained asymptomatic and was enthusiastic in describing his improvement.

DISCUSSION

The frequent association of hypertension and coronary sclerosis is common knowledge.[5–8] With this admission, a definite cause and effect relationship between Ansolysen and myocardial infarction is difficult to establish in our patient. As with any case of hypertension, many immeasurable factors were present. However, we feel the evidence indicates that Ansolysen and the resultant induced relative hypotension certainly were at least strong contributory factors.

Surgeons are aware that elderly patients, and more specifically those with definite coronary artery disease, tolerate lowering of the blood pressure and shock poorly. As a result of the hypotension, myocardial infarction is apt to occur. Myocardial infarction during massive gastrointestinal hemorrhage is a similar problem long familiar to the internist. A review of the literature reveals that successful attempts to drastically lower the hypertensive blood pressure by either surgical or medical means frequently have been complicated by the development of a myocardial infarction. In thoracolumbar sympathectomy[9,10] and sympathectomy plus adrenalectomy,[11] coronary occlusion and angina pectoris are listed as frequent complications in both the operative and postoperative periods.

Myocardial infarction as demonstrated by an electrocardiogram or postmortem examination has been documented as occurring when the hypertensive blood pressure was dropped to normotensive or inadvertently lower levels with hydralazine,[12–14] hexamethonium,[15] and with the combination of hexamethonium and hydrala-

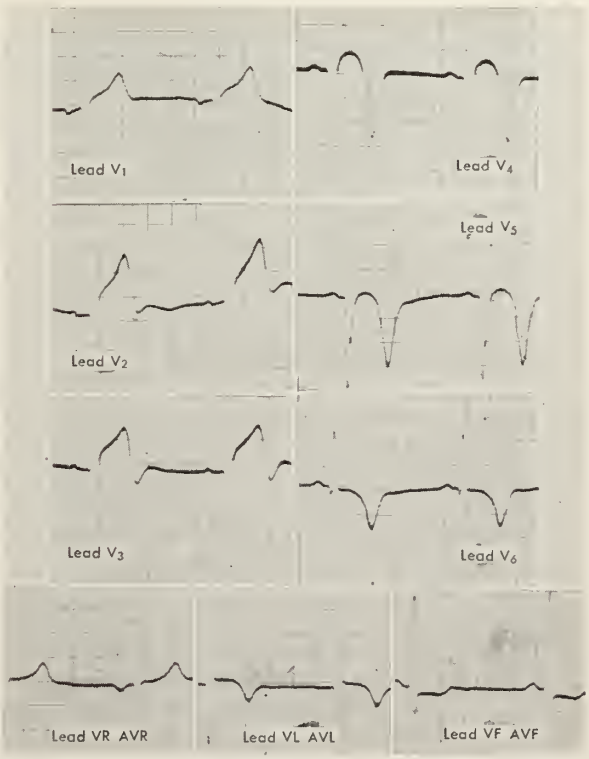

Fig. 2. Electrocardiographic tracing taken shortly after recovery from an acute "heart attack" while on pentolinium and reserpine therapy. A superimposed change due to an anterior wall myocardial infarction is present.

zine.[2] Angina pectoris has been documented as occurring during a hypotensive episode with hydralazine[12,14] and with oral hexamethonium.[16–18] Other reports strongly indict Dibenzyline,[19] hydralazine,[17,20–22] and hexamethonium plus hydralazine[2,12] as the direct or indirect cause of the angina contracted. In addition, electrocardiographic changes suggesting coronary insufficiency but unassociated with chest pain have been reported with Veratrum,[23] hydralazine,[13,19] "688A",[24] and Rauwolfia plus hexamethonium.[21] Maxwell and Campbell[25] found such changes almost constantly in patients with severe hypotension induced by pentolinium tartrate. The probable relationship of the myocardial ischemia or infarction to the antihypertensive drugs is the drastic lowering of the blood pressure which reduces the mean aortic pressure and the coronary blood flow with resultant myocardial anoxemia. It is problematic whether or not this could occur without associated coronary arteriosclerosis, but certainly the possiblity of this occurrence is much greater if this condition is present. Furthermore, in the presence of coronary arteriosclerosis, it is likely to occur with less reduction in pressure. Another factor to be considered is the state of relative myocardial ischemia resulting from increased muscle mass in the pure hypertensive heart with its inability to tolerate severe hypotension. Unlike other antihypertensive drugs, with Dibenzyline or hydralazine usually an associated tachycardia is present. This accounts for the higher incidence of such complications with these drugs. It is generally agreed that the use of these drugs singularly, without some other drug to slow the heart rate, is definitely contraindicated in hypertensive patients in whom coronary artery disease has been demonstrated or might be suspected. Opinion differs as to whether the ganglionic blocking agents, for example, hexamethonium or pentolinium are indicated[18,26] or contraindicated[12] in hypertension complicated by coronary artery disease. However, the consensus indicates that in the absence of a recent myocardial infarction, cautious slow reduction of the blood pressure by the ganglionic blocking agents or other antihypertensive agents will reduce the cardiac work load, relieve angina, and prevent coronary occlusion in a high percentage of cases. Reports of improvement in a significant per cent of hypertensives with angina pectoris after the blood pressure was reduced has been reported with Veratrum,[27] Rauwolfia serpentina,[21] oral hexamethonium,[18,28] hexamethonium plus hydralazine,[13,26] and even hydralazine[22] when the drug could be tolerated for a sufficient period of time.

Doyle[29] has demonstrated that serial electrocardiographic studies afford a useful and objective guide to the effectiveness of blood pressure control. The electrocardiogram usually improves with successful therapy. Other studies previously listed have indicated that patterns of coronary ischemia or greater electrocardiographic impairment often occur before chest pain develops. Case references by Grob and Langford[12] suggest progressive serial electrocardiographic changes may serve as an omen of impending angina pectoris or myocardial infarction. Therefore, the electrocardiogram may be used as a valuable indicator for reduction or discontinuance of potent antihypertensive drugs.

Our patient, in addition to Ansolysen, was receiving another antihypertensive drug, reserpine (Serpasil). This medicament and other alkaloids of Rauwolfia serpentina have been used widely in medicine for several years, and no serious untoward side effects have been reported. Preliminary studies[21,30,31] also indicate they reduce the side effects of other antihypertensive drugs, such as hydralazine, hexamethonium, and pentolinium tartrate. In studying the combined reactions of reserpine and pentolinium tartrate (Ansolysen), Smirk and associates[31] noted that in addition to having fewer of the usual side effects of pentolinium, the effective dose of pentolinium was smaller, fluctuations in blood pressure and postural hypotension were lessened, and casual outpatient department blood pressure readings became more reliable as a guide to dosage. He postulated a synergistic hypotensive effect between the two drugs. Livesay and Moyer[21] indicated that antecedent therapy with the Rauwolfia alkaloids for as long as two to three months before the more potent drugs were used would result in a better stabilized patient and still fewer side effects.

Although pentolinium tartrate produces a more predictable fall in blood pressure than other antihypertensive agents, extraneous factors are present that intensify the hypotensive effect.[32,33] These factors include postural effects, ingestion of alcohol, heavy meals at the height of drug effect, vigorous exercise, rigid sodium restriction, hot weather, and mercurial diuretics. Some inhibition of intestinal motility occurs. The resulting constipation might, therefore, produce an exaggerated response by accumulation of the drug in the gastrointestinal tract. The patient should be made aware of these factors and every effort made to minimize them so that dangerous hypotensive episodes may be avoided. Patients who are feeble, arteriosclerotic, those with previous sympathectomy, or those with im-

paired renal function are prone to be hypersensitive to this drug. On the other hand, of interest to note is the fact that the degree of renal impairment was lessened in some patients.

Nitroglycerin and erythrityl tetranitrate have been reported[12] to potentiate the hypotensive effect of hexamethonium or pentamethonium — "an effect more than additive." A similar effect would be expected with pentolinium tartrate. No studies relative to this were found, but such has been anticipated by Smirk[33] who observed potentiation by other vasodilating influences. If confirmed, this is of importance since a patient who sustains angina pectoris as a result of an induced relative or absolute hypotensive episode could potentiate myocardial anoxemia by nitroglycerin. While on drug therapy for hypertension, our patient took 4 successive nitroglycerin tablets sublingually for a sustained episode of substernal pain. A short time later he proved to have an infarction. Usually the severe hypotensive episodes are postural, and, as a rule, if the patient assumes the Trendelenburg or supine position, no other treatment is necessary.[25] Adrenalin is contraindicated,[25] but norepinephrine by slow intravenous infusion may be used in the more refractory severe hypotensive episodes.[26]

SUMMARY

All of the recent reports on the management of the hypertensive patient with the new and valuable orally administered drug, pentolinium tartrate (Ansolysen), indicate that no serious complications have occurred in patients given this therapy. A myocardial infarction on rare occasions may apparently result from its use. Such a reaction associated with pentolinium therapy in a relatively young male hypertensive without a previous history of angina pectoris is reported. Some probable mechanisms and preventive measures for the condition are discussed.

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Lancet CLINICAL REVIEWS

This department of THE JOURNAL-LANCET *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Chronic Vitamin A Poisoning

A Case Report

ROBERT B. TUDOR, M.D.

Bismarck, North Dakota

THIRTY CASES [1–21] of poisoning due to chronic overdosage with vitamin A have been reported. Josephs[1] reported the first case in 1944, severe hypervitaminosis A occurring in a boy 3 years of age who had received about 240,000 U.S.P. units of vitamin A daily for thirty-three months. The effects of excess vitamin A on animals were first described by von Drigalski,[22] Collazo and Sanchez-Rodriguez,[23] Moore and Wang,[24] and Domagk and von Dobeneck.[25]

CLINICAL FINDINGS

The chief symptoms are a long latent period, irritability, anorexia, scaly skin eruption, pain along the bones most exposed to trauma, swollen legs and forearms, pruritus, alopecia, cracked and bleeding lips, and tender swellings of the skull. Hepatosplenomegaly, hyperpigmentation, persistent severe headache, exophthalmos, papilledema, and a craving for butter may be present. A massive dose of vitamin A may cause an acute, benign hydrocephalus.[26]

RADIOLOGIC FINDINGS

Roentgenograms have shown hyperostoses of the bones involved, occasional mottling of epiphyses, thinning of the calvaria, decalcification of the skull and vertebrae, and calcification of pericapsular structures.

ROBERT B. TUDOR, *a 1938 graduate of the University of Minnesota, is on the staff of the Bismarck and St. Alexius Hospitals and the department of pediatrics, Quain and Ramstad Clinic, Bismarck, North Dakota.*

PATHOLOGY

Biopsy has been done in 2 cases, and has shown thickening of the periosteum with secondary calcification. In rats[27] excess vitamin A has been shown to cause acceleration of periosteal proliferation, rapid consumption of epiphyseal cartilage, and remodeling of bone attended by osteoclasis. Hemorrhages[28] are common in vitamin A poisoning in animals, but are uncommon in humans. They are due to hypoprothrombinemia.

CASE HISTORY

S. M., a 20-month-old white male, was first seen August 13, 1952, because of irritability. His birth weight was 5 lb. 9 oz. He had diphtheria, pertussis, tetanus, and smallpox immunizations before the age of 1 year. He had had no previous illness. On August 3, 1952, he had fever and diarrhea. About August 6, 1952, the mother noted swellings of the occiput. On August 9, 1952, he was given a penicillin shot. Examination revealed that the temperature was 100.8° rectally. The weight was 27½ lb.; the head circumference was 50½ cm. He was a very irritable child. The skin was normal. The glands were not enlarged. Bilateral tender occipital masses and massive temporal craniotabes were present. The hair was sparse. The throat was inflamed. The ears were normal. The heart was normal. The lungs were clear. The liver, spleen, and kidneys were not palpable. The extremities were not tender. The reflexes were normal. Accessory clinical findings showed hemoglobin 74 per cent, white cell count 15,900, polys 13, lymphs 70, and eosinophils 3 per cent. Throat culture showed alpha streptococcus. Blood culture was sterile. Routine agglutinations were normal. Peripheral blood smear was normal. Urinalysis was normal. Blood calcium was 11.5 and phosphorus 5.0. Alkaline phosphatase was 3 King-Armstrong units. Lumbar puncture showed 2 mononuclear cells, normal sugar, and 10

mg. of protein. Roentgenograms disclosed a normal chest, periostitis of the long bones, and thinning of the cranial bones. Bone marrow aspiration was found to be normal.

On August 14, 1952, it was discovered that the child had been taking 1 tsp. a day of Navitol with Viosterol, approximately 200,000 units of vitamin A, since January 1952. Blood vitamin A level was 694 gamma and carotene level was 472 gamma. (Normal level for vitamin A is 20 to 40. Normal level for carotene is 20 to 200.) The child did not crave butter. The Navitol was discontinued and he was discharged from the hospital August 15, 1952.

He was next admitted to the hospital August 19, 1952, because of a head injury. At this time, because of a hemoglobin of 41 per cent, he was given a blood transfusion. Roentgenograms disclosed a fracture of the right parietal bone.

He was next seen September 2, 1952. The head circumference was 50 cm. The hemoglobin was 88 per cent. The weight was 26½ lb. There were no tender swellings of the head. Temporal craniotabes were still present.

On January 13, 1953, the temperature was 99.4° rectally. The weight was 28 lb. The head circumference was 51 cm. The hemoglobin was 72 per cent. There was no craniotabes. The vitamin A level was 37.8 gamma per cent. The carotene level was 468 gamma per cent.

On June 29, 1953, the weight was 32 lb. There were no complaints and no unusual physical findings. The vitamin A level was 38.5 gamma per cent and the carotene level was 396 gamma per cent.

DISCUSSION

The toxic factor in vitamin A poisoning is said to be the permanently elevated plasma vitamin A level. Clinical hypervitaminosis A develops only after the liver is loaded with the vitamin so that it is no longer able to remove from the circulation the excess amount ingested. Hepatic dysfunction may be the basis for the vitamin A poisoning. Faulty or limited excretion may contribute to maintenance of high blood levels.

SUMMARY

The case of a 20-month-old child who developed signs of vitamin A poisoning after ingesting 200,000 units of vitamin A daily for eight months has been discussed. Craniotabes which occurred in this patient has been reported in the literature in only 1 other patient with vitamin A poisoning.[11]

ADDITION

Since the preparation of this paper, German has reported the case of an adult who developed astereognosis and onycholysis after taking 50,000 to 100,000 units of vitamin A daily for eight months, in Queries and Minor Notes, J.A.M.A. 155:947, 1954.

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Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns. Proceedings of the Association, December 11 and 12, 1953. New York, Baltimore: Williams and Wilkins Co. 425 pages. $10.00.

For anyone interested in genetics and inheritance and also in environmental effects, this book will be invaluable. As always in this series of researches, the articles were written by nationally known experts. Included in the volume are subjects such as Principles of Human Genetics, Genetics and Physiology of the Nervous System, Genetic Factors Which Affect the Susceptibility and Resistance of the Nervous System to Virus Diseases, and Inherited and Acquired Components of Behavior. There is even an article on the Prenatal Affects of Nutrition. Also included are articles on behavior patterns and early human fetal behavior.

Today many investigators will be much interested in the chapter by Herndon on the Genetics of Lipidoses. Many abnormalities of brain function appear to be due to hereditary disturbances in the chemistry of the brain. These defects are particularly well covered in the article Phenylpyruvic Oligophrenia. As many persons know today, infants who lack the ability to handle phenylpyruvic acid are always mentally undeveloped.

There is a good article on The Inheritance of Neuromuscular Disorders, and one on Hereditary Ataxias. Seizures, brain waves, and intelligence in epileptic twins are also discussed.

Also included are discussions of the genetics of psychotic behavior patterns and the genetic aspects of adaptability.

This book ought to be read by all thoughtful physicians. It certainly ought to be read by all psychiatrists.

WALTER C. ALVAREZ, M.D.

•

Ageing—General Aspects. Ciba Foundation Colloquia on Ageing—Vol. 1, edited by G. E. W. WOLSTENHOLME and MARGARET P. CAMERON. Boston: Little, Brown & Co. 225 pages. $6.75.

This volume is a presentation of the papers and discussions of 34 participants in a Ciba Foundation Symposium in July 1954 on Ageing, dealing with its general aspects. Many of the leading scientists in gerontology participated and the essays constitute a major contribution to the current literature in the field. Much attention was paid to chemical and histochemical studies of tissues and organs in relation to age. A healthy emphasis was placed upon the importance of the study of changes in frequency of various types of disease resulting from changed circumstances in ageing studies in experimental animals. Organisms still die of specific disease processes in old age and longevity studies must include observations on shifts in major causes of death to be significant.

Another important point brought out is that the current assumption in child-feeding that fast growth rates are desirable, may be quite fallacious. To the contrary, it may be entirely possible that early *underfeeding*, especially in calories, would be much more conducive to a healthy long life.

This volume is well illustrated, documented, and indexed and should be of interest to every student of the ageing problem.

MAURICE B. VISSCHER, M.D.

•

Normal Labor, by LEROY A. CALKINS, M.D., 1953. Springfield, Illinois: Charles C Thomas. 128 pages. Illustrated. $4.00.

The first half of this monograph represents original writing for this publication; the latter half consists of reprints of previously published material.

The former is a review of the author's twenty-five years of experience and deals with labor, including the author's thoughts on etiology of the onset of labor and studies of the first, second, and third stages of normal labor.

The author feels that the etiology of onset of labor is divided into a neurogenic phase and estrin-progestin balance phase. The accumulation of actomyosin to the point of initiating contractions may be of importance.

In determining the end of the first stage, the author stresses not only complete dilation but more important, complete retraction of the cervix. Frequency and intensity of contractions, not duration of a single contraction, are important in determining the effectiveness of labor. Determination and classification of the above are discussed. A rather cumbersome and lengthy method of predicting length of labor is detailed.

A modification of Williams' technic for management of the third stage of labor contains much valuable information.

The author, suprisingly, leaves the problem of breast feeding and circumcision of the male infant to the pediatrician.

The latter half of the monograph is made up of 7 previously published papers which enlarge on certain phases of labor.

JAMES R. BERGQUIST, M.D.

•

Hysterectomy, by JOHN C. BURCH and HORACE T. LAVELY, 1954. Springfield, Illinois: Charles C Thomas. $5.50.

This small volume of 85 pages is another of the monographs of the American Lecture Series. The authors are professor and instructor, respectively, of gynecology at Vanderbilt University School of Medicine. A discussion of the general philosophy of hysterectomy is presented, its indications, and the technic as used by the authors. Complications of surgery are also discussed.

Some biostatistic evidence as to the future risk of destruction by uterine cancer is given and discussed in its relation to clinical decisions in the handling of such conditions as "functional uterine bleeding." In general, the authors' conclusions concerning indications are those which are generally accepted. The surgical technics vary little from those usually applied except that in both abdominal and vaginal hysterectomy, the vagina is not closed.

A good deal of opinion and argument are expressed, but unfortunately little in the way of proof is presented. In general, however, it is a clear and logical exposition of the problems concerned.

The volume is attractively printed on glossy paper which takes the illustrations well. An extraordinary number of excellent illustrations of surgical technics are included which were produced by Helen Lorraine. These illustrations will be useful both for teaching and for the beginner.

J. L. MCKELVEY, M.D.

Transactions of the North Dakota State Medical Association

Sixty-Eighth Annual Meeting

Bismarck, North Dakota, April 30, May 1, 2, and 3, 1955

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Sixty-Eighth Annual Meeting

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PROCEEDINGS OF THE HOUSE OF DELEGATES

of the North Dakota State Medical Association

Sixty-Eighth Annual Meeting

First Session, Saturday, April 30, 1955

The first session of the House of Delegates of the North Dakota State Medical Association was called to order by the Speaker of the House, Dr. G. A. Dodds, at 4:30 P.M. at the Prince Hotel, Bismarck, North Dakota, April 30, 1955.

Dr. E. M. Haugrud, chairman of the Credentials Committee, reported that a quorum was present and all credentials were in order. The secretary, Dr. E. H. Boerth, called the roll and the following doctors responded:

William Fox, Rugby; E. J. Schwinghamer, alternate, New Rockford; E. M. Haugrud, Fargo; Frank M. Melton, Fargo; R. D. Weible, Fargo; L. E. Wold, Fargo; H. W. Hawn, Fargo; A. C. Burt, alternate, Fargo; R. C. Painter, Grand Forks; John Sandmeyer, Grand Forks; F. A. Hill, Grand Forks; A. C. Kohlmeyer, Larimore; Bruce Boynton, Grafton; W. C. Dailey, alternate, Grand Forks; A. R. Sorenson, Minot; G. M. Hart, Minot; A. F. Hammargren, Harvey; F. R. Erenfeld, Minot; V. J. Fischer, Minot; G. Christianson, alternate, Valley City; M. S. Jacobson, Elgin; Carl Baumgartner, Bismarck; O. C. Gaebe, New Salem; R. O. Saxvik, Jamestown; C. H. Peters, Bismarck; Robert Gilliland, Dickinson; Keith Foster, Dickinson; Julien Tosky, alternate, Hebron; T. E. Pederson, Jamestown; John Van Der Linde, Jamestown; Keith Vandergon, Portland; J. D. Craven, Williston; and Robert McLean, alternate, Hillsboro.

Thirty-three delegates were present and the Speaker declared a quorum.

A motion was made and seconded that the reading of the minutes of the last session be dispensed with and that they be accepted as printed in THE JOURNAL-LANCET.

It was moved by Dr. Haugrud and seconded by Dr. Peters that the reports of the president, secretary, executive secretary, and treasurer be referred to Committee number 1. Motion carried.

REPORT OF THE PRESIDENT

The many other reports in this Handbook will give detailed information regarding the activities of the state association during the past year. I would like to call your attention to a few things which to me appear to be of particular importance.

During the year it has been my pleasure to attend meetings of the First, Sixth, Traill-Steele, Devils Lake, and Grand Forks District Societies. I found these meetings to be all well attended and the membership demonstrating an interest in the affair of the state association. Questions at these meetings and elsewhere indicate there is still considerable lack of knowledge on the part of the general membership regarding the activities of the state association. I am satisfied that increased efforts to inform the general membership as to the scope of our activities are essential to maintain continuing and increasing interest. Such efforts would appear to be the function of the president, the executive secretary, and the various councillors, and could well be a high priority project for the coming year.

The problems which seem to me most important are all related in some measure to public relations and information. Our present Public Relations Program should be continued and steadily expanded. In the past this work has been under the direction of the Committee on Public Policy and Legislation, and, as a result, during legislative years the public relations portion of the program has tended to lag. Accordingly, it would appear that consideration should be given to a separate committee on Public Relations and Information to direct

such an expanding program in cooperation with the executive secretary.

We were successful this past year in influencing legislative action in certain fields and the executive secretary and the Committee on Public Policy and Legislation are to be highly commended for their excellent work in this regard. It was obvious during this and past legislative sessions that the influence of the individual physician on his senators and legislators can be great. If we are to continue to be successful in this field, public relations work must be continued throughout the state not only by an active committee in this field but by the individual efforts of all practicing physicians.

Our past legislative activities have practically all been in opposition to proposed legislation. The time may be here for us to assume a positive attitude in proposing new legislation and improvement in present laws. It is probably also time for a similar positive attitude on the part of the state association and the local societies in regard to state and community affairs in general.

We must continue and step up our efforts to persuade young physicians to enter practice in the smaller communities throughout the state. While many doctors have settled in smaller communities during the past few years, still too many areas are without the services of a physician and there are a number of areas in which additional physicians would be advisable. The people in some of these areas are having difficulty understanding why they have been unable to secure services of a physician. They must either understand the situation or a physician must be brought into the community or they may look to other sources for their medical care. Our cooperative program involving the office of the executive secretary and the Committee on Rural Health should be continued, and consideration might be given to specific efforts to inform the students in our own medical school of the compensations and advantages of practice in rural areas of North Dakota.

Our Blue Shield Program is a most serious problem which still receives generous criticism from physicians around the state. Much of this criticism is no doubt justified but much of it is not, and the faults are largely our own. In contrast to the situation in some other states, all members of our Blue Shield board of directors are doctors elected by doctors. District societies must be diligent in electing representatives to the Blue Shield Corporation and in insisting that these representatives attend the corporation meetings for the purposes of electing the board of directors and reporting the ideas of the doctors in their district regarding the policies and operation of Blue Shield. Our Committee on Prepayment Medical Care must give continuous and close attention to both the Blue Shield Program and to the various commercial insurance programs throughout the state. One of the most serious problems with prepayment insurance programs is the inadequate policy which is oversold and held to offer protection that is not reflected in the performance of the company upon claims. Such policies hamper the whole prepayment program and may lead to distrust by the public of all prepayment plans. The answer to this problem is not clear as yet but might be found through joint discussions with reputable insurance people possibly through their state organizations.

We received a communication from representatives of the North Dakota State Bar Association requesting a committee to meet with them in a cooperative venture to discuss and make plans to solve difficulties and problems which at times arise between the medical and legal professions. Believing that most such difficulties are misunderstandings and that physicians, as citizens possessing special knowledge which is essential to the proper settling of many legal problems, must cooperate with the legal profession and the courts, I appointed such a committee.

Officials of the state hospital association also requested a liaison committee to meet with a similar committee from their group to consider mutual problems. Such a committee was also appointed.

We have agreed to hold the 1956 session in Aberdeen, South Dakota, in cooperation with the South Dakota State Medical Association to commemorate the seventy-fifth anniversary of the founding of the first medical society in Dakota territory. A special committee from your society was appointed during the past year and has already engaged in discussions with a similar committee from South Dakota on arrangements for that meeting and the Scientific Program. We should make every effort to make that meeting a success. Near the close of the 1954 session of the House of Delegates, it was voted to hold the 1956 annual meeting of the Council and House of Delegates in the state of North Dakota prior to the meeting in Aberdeen. In my opinion this was ill-advised and a hasty decision which should be revoked at this session.

The various sections on membership of our Constitution and By-Laws are not entirely clear. Consideration should be given to a committee to clarify all these sections. Consideration might also be given as to the advisability of a permanent committee on Constitution and By-Laws. The secretary and the Speaker of the House might be valuable members of such a committee.

Many men have devoted much time to the conduct of our affairs during the past year. I wish to extend my personal thanks to all of these for their time, effort, and cooperation, to thank and commend Mr. Lyle Limond for his great help and diligence, and to thank all of the members for allowing me to represent them and attempt to direct our affairs during the past year.

P. H. Woutat, M.D., President

SECRETARY'S REPORT

MEMBERSHIP: The total membership for 1954 was 411. Of this number, 378 paid the regular membership fee, 12 were on a retired or limited basis, and 15 were honorary members. Six members were carried on a complimentary basis due to military service and age. Eleven members passed away during the year and several have left the state. New members, however, are being steadily added to our roster.

Table 1 shows the annual membership for the past eight years. From this table one can see that the membership shows a slow but appreciable gain since 1947.

TABLE 1
COMPARISON OF ANNUAL MEMBERSHIP

	1947	1948	1949	1950	1951	1952	1953	1954
Paid memberships	342	356	364	356	362	362	368	378
Honorary memberships	8	5	13	12	11	10	12	15
Retired and limited							13	12
Dues cancelled, military service, and age exemption	4	–	–	–	11	12	16	6
	354	361	377	368	384	384	409	411

Table 2 shows the annual dues for 1955, which are coming in quite promptly. There are still a number of members, however, who have not as yet paid their 1955 dues and the District Medical Society secretaries and councillors are urged to use every possible means to collect the dues of these delinquent members.

TABLE 2

	April 15 1949	April 30 1950	April 30 1951	April 15 1952	April 20 1953	April 10 1954	April 8 1955
Paid-up members	302	309	307	249	296	323	323
Honorary members	9	11	11	8	9	13	14
To be honorary	4	1	2	2	3	4	3
Dues cancelled, military service				11	12	4	3
Limited						1	1
Retired						7	7
	315	321	320	270	320	352	351

STATE ASSOCIATION MEMBERSHIPS

	1954 Reg.	1954 Rtd.	1954 Hon.	1955 Reg.	1955 Rtd.	1955 Hon.
First	75	1	4	75		3
Devils Lake	26		3	22		2
Grand Forks	69		2	52		2
Kotana	17			14		
Northwest	58	1	2	39		3
Sheyenne Valley	10	1		9	2	
Sixth	60	5	3	49		3
Southwestern	23	3		22	3	
Stutsman	30		1	32	1	
Traill-Steele	10	1		9	1	1
	378	12	15	323	7	14
	390			330		

A.M.A. GENERAL MEMBERSHIPS

	1954	1955
First	72	73
Devils Lake	25	22
Grand Forks	59	48
Kotana	17	14
Northwest	58	39
Sheyenne Valley	10	9
Sixth	56	47
Southwestern	14	4
Stutsman	30	32
Traill-Steele	9	9
	350	297

Three of the societies show a paid-up membership roster for the current year, but others have forwarded only partial reports. The Constitution and By-Laws of the North Dakota State Medical Association states that such dues should be forwarded the state office not later than March 1 of the current year, and, due to the press of work in the state office prior to the annual meeting, it would be extremely helpful to the office staff if a majority of the membership dues were processed earlier in the year. It should be noted that, although March 1 is the stipulated date for the receipt of dues, this report is shown as April 8 to give an up-to-date picture of paid memberships.

The secretary has kept in touch with the operations of the state office and wishes to commend Mr. Limond and Mrs. Fremming for their excellent work.

E. H. Boerth, M.D., Secretary

EXECUTIVE SECRETARY'S REPORT

MEETINGS: Your executive secretary attended several meetings in behalf of the association and made many personal contacts with individual physicians, newspaper editors, legislators, radio station personnel, hospital administrators, nurses, dentists, and others. A rather complete listing will be found in the Travel Log of the executive secretary a little further on in these pages.

I was fortunate in being able to attend at least 1 meeting in 9 of the 10 district medical societies last year.

The School Health Lectures were again presented in cooperation with the North Dakota State Dental Association at the 5 Teachers Colleges. Dr. P. H. Woutat lectured at Mayville, Dr. O. W. Johnson at Minot, Dr. W. H. Gilsdorf at Valley City, Dr. A. E. Spear at Dickinson, and Dr. Ellis Oster at Ellendale.

The third annual Medical-Press-Radio Conference was held in Grand Forks on September 25, 1954. This year the North Dakota Hospital Association joined us after securing permission from the council. They entered on a fifty-fifty basis as to expenses. From comments received by those in attendance, it can be considered a successful venture.

It is still felt that some of the committees are not too active. Your state office continues to aid in the work of those committees which are active. Your executive secretary was, with one exception, present at all committee meetings. It is again suggested that the committees meet in the fall and early winter months. If this is done, it will facilitate getting out the Handbook during the first two weeks in April. It is further suggested that all committee reports be sent in to the state office by March 15 so that the printing of the Handbook can be expedited.

STATE OFFICE: As of April 30, 1955, the office of the Veterans Medical Service Division of the North Dakota State Medical Association will cease to exist. The Home Town medical care program for the veteran will be handled by the VA office in Fargo. Our job as a processing center for authorities and vouchers will end. The association continues its liaison activities with the VA through our Sub-Committee on Veterans Medical Service under the able chairmanship of Dr. Robert B. Radl. Please note Dr. Radl's report in this Handbook.

Your headquarters' office is continuing in its efforts to be of even greater service to the total membership, to public and private health agencies, and to the public in general.

As you all know, it is from here that the membership Newsletter and the Auxiliary's Newsletter is processed; the Veterans Medical Service Division has been discharging its duties; the Physicians' Placement Bureau functions; the State Board of Medical Examiners' annual license renewals are handled; committee meetings are arranged and members notified; annual association and A.M.A. dues are processed; disbursement of Uniform Insurance Reporting Forms is recorded; and many other duties too numerous to mention.

LEGISLATION: Your executive secretary came through his second legislative session, since coming to North Dakota, without too many scars from the crossfire in the Senate between the Coalition and ROC forces. I again spent practically twelve to fifteen hours a day with our elected representatives as I did in 1953. I feel that this is necessary as the representative of the "Medical Trust" (as was said on the floor of the House) in order to make friends and acquaintances among our legislators. The busy doctor cannot find the time to be present at the Capitol Building in Bismarck. I hope to have a chance of giving a complete verbal account of my activities at this past thirty-fourth Legislative Assembly before the Council and House of Delegates. I am giving but a brief outline of some of the bills of interest to medicine. To do otherwise, would increase the size of our Handbook unduly.

I do not honestly believe that medicine was harmed or set back appreciably in its program of providing ever-improving health care to all the people of North Dakota, by the past legislative session.

Your president, plus Drs. McCannel, O. W. Johnson, Saxvik, Paul Johnson, Peters, C. C. Johnson, Percy Owens, and others visited the Capitol and met with certain of the legislators plus appearing before committee hearings. Drs. P. H. Woutat, O. W. Johnson, and C. H.

Peters did a fine piece of work in appearing before the House General Affairs Committee in opposition to HB 834, the Osteopathic Bill. It was defeated in committee even though a Chicago attorney had been flown in by the osteopaths.

Listed below are the 8 House Bills, 7 Senate Bills and 1 House Concurrent Resolution which we followed rather closely. This listing does not include the bills dealing with the State Health Department or the institutions like Grafton, the State Hospital, and so on.

SENATE BILLS:

SB 18 (Special education for exceptional children). Budget Board had approved appropriation out of Equalization Fund of $164,000. Senate raised this $50,000, and the House added another $50,000. Total—$264,000. We supported this bill. Governor signed it.

SB 61 (Narcotic privileges and surgical chiropodists). Adds doctors of surgical chiropody to practitioners who may use narcotic drugs in professional practice. We opposed this bill and lost. Governor signed it.

SB 117 (Anti-fluoridation). We opposed this bill and it was killed in committee.

SB 125 (Coroners to be physicians). Coroners to be appointed by county commissioners in only those counties of 8,000 population or more, of which there are 29. This bill was not sponsored by the North Dakota State Medical Association, but it was felt that it was a step in the right direction. Governor signed it.

SB 155 (Pharmacy bill). Amends law regulating sale of narcotic drugs to permit a druggist to sell them on oral prescription of doctor, dentist, or veterinarian in compliance with new federal regulations. We were interested. The Governor signed it.

SB 165 (Pharmacy bill). Would have allowed a limitless number of pharmacies. It was introduced by Senator Shrock in opposition to HB 791. We were interested but took no overt action. It lost.

SB 188 (Arbitrary fixing of medical and hospital fees by State Welfare Board). We opposed this bill and it was killed in committee.

HOUSE BILLS:

HB 661 (Nurse preparation scholarships). We were interested but took no overt action. Governor signed it.

HB 664 (Licensing of masseurs). We were quite interested but took no overt action. It lost.

HB 668 (Optometrists). Raises regstration fees for optometrists and increases compensation of the state Board of Optometrists plus redefining the definition of optometrists. We supported this bill after checking with the North Dakota Academy of O. and O. Governor signed it.

HB 735 (Medical examinations for school teachers). It lost.

HB 750 (Chiropractic scholarships). We were quite interested but took no overt action. It lost.

HB 765 (Pharmacy bill). The so-called "aspirin bill." Would have allowed the sale of aspirin and similar medications in grocery stores, and so forth. We followed the bill. It lost.

HB 791 (Pharmacy bill). Would have limited the number of pharmacies. We were interested but took no overt action. It lost.

HB 834 (Osteopath bill). Would have given full drug and surgical privileges with instruments to osteopaths. We opposed this bill strenuously. It was killed in committee.

HCR-Z (State health and accident insurance). Directed the Legislative Research Committee to study the feasibility of a state-operated health and accident insurance system patterned after the one in Saskatchewan. We opposed this resolution. It lost hy a voice vote in the House.

I am pleased to report that during this Legislative Session we were able to have a better working program regarding contacts with the legislators by physicians than we had in 1953. You must realize that there is a great deal yet to be done in this regard. The physician should not continue to say that he does not want to be or cannot be concerned with politics. We must have a goodly number of our members willing to fight for their convictions. If this is not done or readily understood, we are going to be in for a rude awakening some fine day and find that the medical profession has been legislated right down the drain.

It is again suggested that our councillor districts become tight political entities in regard to contacts with the legislators. Our elected representatives must have an awareness of their medical constituents' thinking on legislation pertaining to health, education and welfare.

PHYSICIANS' PLACEMENT SERVICE: Seventeen North Dakota communities and 16 physicians or groups have contacted this office up to March 1, 1955, regarding the securing of physicians.

Several avenues of publicity have been used in alerting the public that the North Dakota State Medical Association is offering this service.

Inquiries by letter have been received from 51 physicians during this past year regarding openings in our state.

The 17 communities seeking a physician or additional physicians are as follows: Anamoose, Belfield, Buffalo, Fairmount, Fessenden, Finley, Goodrich, Grenora, Hettinger, Hope, McClusky, McHenry, Milnor, Mohall, Napolcon, Pembina, and Strasburg. The 4 towns of those listed above having a physician, but wanting 1 or more are Fessenden, Hettinger, Mohall, and Napoleon.

This office, as of March 1, 1955, has received word that 3 physicians have been placed because of the physicians' placement service.

ANNUAL SESSION: Your executive secretary wishes to thank Dr. Robert Nuessle, general chairman, the chairmen and members of the several committees, plus other members of the Sixth District Medical Society with whom he has worked in connection with the 1955 annual meeting.

It should be noted that the annual meeting continues to operate with a deficit, although we have added one or two firms each year to our list of technical exhibitors plus raising the price charged for exhibit space. The amount of deficit has declined each year, since the Fargo meeting in 1952, to the modest sum of $155.82 for the 1954 meeting in Grand Forks. It is not anticipated that the present meeting in Bismarck will equal or improve on the above-mentioned deficit figure.

THE TRAVEL LOG:

1954—

May 12-14—Jamestown. Attended the annual meeting of the North Dakota Public Health Association.

May 23-26—Bismarck. Attended the annual meeting of the North Dakota State Dental Association.

May 27—Jamestown. Attended a meeting of the Stutsman County District Medical Society.

June 1-6—St. Paul. Attended the annual meeting of the Middle States Public Health Association.

June 14—Bismarck. Attended the Governor's Safety Conference.

June 15—Bismarck. Attended the meeting of the State Health Council.

June 16-18—Grand Forks. Met with Dr. Woutat on committee appointments and attended the School Health Workshop.

June 30—Fargo. Called on Drs. Lancaster and Sedlak. Visited the Blue Cross and Blue Shield offices. Contacted R. A. Sand, D.D.S., Legislative Chairman of the North Dakota State Dental Association.

July 1—Wahpeton, and Fairmount. Called on Dr. Bateman and H. H. Pfister, D.D.S. Contacted Mr. E. W. Schouweiler and Mr. Jerry Johnson regarding Physician Placement services.

July 2—Valley City, and Enderlin. Called on Dr. W. H. Gilsdorf. Visited Dr. and Mrs. S. C. Bacheller.

July 7-11—Hillsboro, Portland, and Grand Forks. Contacted Drs. Syver Vinje and McLean. Visited with Miss Wright, superintendent of the Hillsboro Hospital. Called on Dr. Vandergon. Secured final committee appointments from Dr. Woutat. Met with Messrs. Bakke and Logan, Drs. Woutat and Haunz regarding Blue Shield matters. Attended the special meeting of the Council, the Medical Board and the Advisory Council to the Medical Center meetings.

July 21-23—Kenmare, Rugby, and Minot. Called on Dr. and Mrs. Halliday, Drs. McCannel, A. R. Sorenson, O. W. Johnson, Wm. Fox, C. G. Johnson, Devine and Kermott. Visited with Frank Hornstein, publisher of the Pierce County Tribune, and Arne Bjorke, administrator of the Good Samaritan Hospital in Rugby.

July 28-30—Richardton, Dickinson, Bowman, and New Eng-

land. Called on Drs. Moses, C. R. and Ralph Dukart, Gilliland, Gilsdorf, Guloien, Rodgers, Larson, Gumper, Spear, D. J. and H. L. Reichert, Boulding, Denser and Curiskis. Met Sister Helen, administrator of the hospital in Bowman.

August 4—Bismarck. Met with Drs. Radl, Henderson, Kucera, McCarthy and Mr. Pool regarding the Veterans Administration and the Veterans Medical Care program.

August 9-11—Fargo, and Wahpeton. Met Mr. Aubrey Gates, field director of the Council on Rural Health of the A.M.A. and attended a meeting with him and Mr. E. J. Haslerud, director of extension services, N.D.A.C. Called on Drs. Sedlak, Lancaster, Gillam, Strinden, LeMar, Dodds, Fortney, Darner, et al. Visited Dr. Winge and welcomed him to Wahpeton and North Dakota.

August 12—Minot. Called on Vic Corbett, D.D.S., president of the North Dakota State Dental Association. Met Mr. Aubrey Gates and drove him to the airport in Bismarck.

August 18—Grand Forks. Met with Drs. Woutat, Witherstine, Harwood, Porter and Leigh regarding plans for our Third Annual Medical-Press-Radio Conference.

August 19—Grafton, and Park River. Contacted Dr. Glaspel, Dr. Boynton, Dr. Teevens, Dr. Piltingsrud and John Morgan of the newspaper in Grafton, regarding the Medical-Press Conference. Called on Tom Kelley of the newspaper in Park River, and Dr. Piltingsrud, and Sisters Bernadette, Bernardine and Pauline at the hospital in Park River regarding the Conference. Visited with Miss Elsie Catherwood, city auditor in Park River and Dr. Piltingsrud regarding Physician Placement services.

August 20—Pembina, Hamilton, Walhalla, and Cavalier. Contacted Ione DeFrance of the Pembina New Era, Everett Knudson of the Walhalla Mountaineer, Dr. Landry, the Cavalier Chronicle offices and Mrs. Ruby Meisenholder, administrator of the Pembina County Memorial Hospital concerning the Conference. Visited with Senator Franklin Page in Hamilton.

August 21—Grand Forks. Contacted Drs. Muus, Moore, Woutat, Jim Leigh, Liebeler, Hill, et al., regarding the Conference.

August 30—Fargo. Attended a meeting of the Blue Cross and Blue Shield people and the Nodak Mutual agents.

August 31 - September 3—Chicago. Attended the A.M.A.'s PR Institute.

September 8—Jamestown. Attended a meeting of the State Health Council.

September 10—Bismarck. Attended tbe Regional Meeting of the American College of Physicians.

September 16-18—Kenmare, and Williston. Called on Drs. Halliday and Gammell. Attended the meeting of the North Dakota Ob. and Gyn. Society.

September 24—Bismarck. Met with Byron Jackson, president of the North Dakota Hospital Association, Gene Bakke, executive secretary of said Association and Mr. Robert Bilstein, administrator of the Bismarck hospital. I also met with Mr. Leo Brown, director of public relations of the A.M.A. and talked over the next evening's Medical-Press Conference, since he was our speaker.

September 25—Grand Forks. Attended the third annual medical-Press-Radio Conference. The Hospital Association joined us in this venture for the first time.

September 27—Fargo. Attended a meeting of the First District Medical Society with Drs. Woutat and Glaspel. Also attended a special meeting of the Board of Medical Examiners.

September 29—Bismarck. Attended a meeting of the Governor's State Health Planning Committee.

October 4—Fargo. Contacted Drs. Sedlak and Lancaster and visited the offices of Blue Cross and Blue Shield.

Otcober 5—Valley City. Attended the annual meeting of the North Dakota State Nurses Association.

October 6—Valley City, and Devils Lake—Attended Nurses Convention and a meeting of the Devils Lake District Medical Society.

October 7—Jamestown. Attended a meeting of the Stutsman County District Medical Society.

October 8-9—Bismarck. Attended the seventh annual meeting of the North Dakota Society for Crippled Children and Adults.

October 10—Valley City. Attended the dedication ceremonies for the Chronic Disease Hospital and heard a very fine address by Congressman Walter Judd.

October 12—Bismarck. Attended a meeting of the Sixth District Medical Society.

October 13—Mandan, and Elgin. Attended a meeting of the Finance Committee of the North Dakota Mental Health Association and the farewell party for Dr. Jose Bahamonde.

October 19—Bismarck. Attended a meeting of the Lewis and Clark District Nurses Association.

October 25-29—Fargo, Grand Forks, and Grafton. Field trip into the First, Traill-Steele, and Grand Forks District Medical Societies contacting officers and delegates of the three societies.

November 3-5—Minot, and Rugby. Contacted Drs. A. D. McCannel, O. W. Johnson, Keller, Kermott, et al. Attended a meeting of our committee on Mental Health as well as the second annual meeting of the North Dakota Mental Health Association.

November 8—Bismarck. Attended a meeting of the Sixth District Medical Society.

November 9—Dickinson. Attended a meeting of the Southwestern District Medical Society.

November 12-14—St. Paul. Attended the meeting of the North Central Medical Conference.

November 18—Valley City. Attended a meeting of the Sheyenne Valley District Medical Society.

November 20—Fargo. Attended a meeting of the Blue Shield Board of Directors to which our Sub-Committee on Prepayment Medical Care was invited.

November 22—Bismarck. Met with Dr. and Mrs. A. E. Spear, Jim Moore and O. S. Trom of the North Dakota State Pharmaceutical Association and S. Ross Pond of the American Diabetes Association.

November 23—Bismarck. Attended a meeting of the Governor's State Health Planning Committee.

November 24—Bismarck. Attended a meeting of the State Health Council.

November 27—Bismarck. Attended the first annual meeting of the North Dakota Chapter of the American College of Surgeons.

December 7—Bismarck. Attended a meeting of the Sixth District Medical Society with Drs. Woutat and Harwood.

December 10-12—Fargo. Attended the Interim Meeting of the Council and meetings of several Association committees as well as a meeting with the representatives of the North Dakota State Pharmaceutical Association.

December 15—Grand Forks. Attended the testimonial dinner put on by the Grand Forks District Medical Society for Dr. Saiki's completion of twenty-five years at the School of Medicine, University of North Dakota.

1955—

January 6-8—Grand Forks. Attended the meetings of the Board of Medical Examiners.

January 12-14—Fargo. Attended the North Dakota Hospital Association Workshop.

January 15—Grand Forks. Attended a meeting of the Advisory Council to the Medical Center.

January 4-31—Bismarck. With the exception of the above-noted dates, I was lobbying at the thirty-fourth Legislative Assembly.

February 1-28—Bismarck. With the exception of the below-listed dates in February, I was at the Capitol.

February 22—Bismarck. Attended the meetings of the Sixth District Medical Society and its auxiliary, where I spoke on Legislative Highlights.

February 23-27—Milwaukee. Attended the tenth annual meeting of the Rural Health Conference of the A.M.A.

March 1-7—Bismarck. At the Capitol, finishing my lobbying chores.

March 9—Bismarck. Attended combined meeting of committees on Public Health and Maternal and Child Welfare with State Health Department to discuss 1955 Salk vaccine program.

March 12—Fargo. Attended a meeting of the Blue Sbield Board of Directors.

March 23—Minot. Attended the Cancer Seminar of the Northwest District Medical Society.

March 24—Devils Lake. Attended the Cancer Seminar of the Devils Lake Region District Medical Society.

March 25—Grand Forks. Attended the Cancer Seminar of the Grand Forks District Medical Society.

March 28—Fargo. Attended annual meeting of the North Dakota Public Health Association and the Cancer Seminar of the First District Medical Society.

March 29—Fargo. Attended the annual meeting of the North Dakota Public Health Association.

March 30—Jamestown. Attended the Cancer Seminar of the Stutsman County District Medical Society.

March 31—Bismarck. Attended the Cancer Seminar of the Sixth District Medical Society.

April 1—Dickinson. Attended the Cancer Seminar of the Southwestern District Medical Society.

April 14-15—Dickinson. Attended the annual meeting of the North Dakota Press Association.

April 16—Bismarck. Attended the annual meeting of the North Dakota Tuberculosis and Health Association.

April 25—Bismarck. Spoke at the Bismarck Lions Club on Physician Placement services of the North Dakota State Medical Association.

April 26-27—Minot. Attended the annual meeting of the North Dakota Hospital Association.

FINANCE: The Treasurer's report shows a definitely improved balance. This has been caused by the increase in dues which the House of Delegates voted at the 1954 meeting in Grand Forks. To date there has been no mortality as to membership because of this increase. The rate of collections by the district societies increased during January and February of this year as compared to the same months of 1954. We are now receiving dues at, what I charitably call, the normal rate. Stutsman County, Cheyenne Valley, and Traill-Steele district societies were paid up 100 per cent on or before the first week in April of this year. The status of the remaining district societies regarding payment of dues as of April 7, 1955, was as follows:

District	*Number of unpaid members*
Southwestern	2
Kotana	3
Devils Lake	4
First	4
Grand Forks	15
Sixth	17
Northwest	21

It should also be pointed out that when you note the item of receipts from dues in the Treasurer's Report, that this sum is derived from the collection of the remaining 1954 dues which were unpaid as of April 1, 1954, plus the dues already collected for 1955, up to and including March 31, 1955.

The Special Disability Insurance Plan of the North Dakota State Medical Association: During the past year, there was an increase of 33 members to the plan, making a total of more than 50 per cent of our physicians enrolled.

I have been informed by the agent for this plan that the exact number of our members enrolled is confidential. This statement seems a little odd to me. We are all aware that 50 per cent of our members *must* be enrolled. What is so harmful or secret about the total number presently enrolled?

THOUGHTS FOR THE FUTURE:

1. The Council of the North Dakota State Medical Association to be the Grievance Committee in problems arising between physicians and the public and among physicians if these problems cannot first be resolved at the local society level.

2. The formation of a committee in the field of school health.

3. A survey to be made of the utilization of prepayment medical care plans in North Dakota.

4. The formation of a separate committee on Public Relations and Education and the maintaining of a Committee on Legislation active year in and year out.

5. Consideration should be given to Dr. O. W. Johnson's request that our association become a sponsor in the National Essay Contest of the Association of American Physicians and Surgeons.

6. Consideration of the suggestion to change our association's fiscal year to January 1 through December 31.

7. The formation of a standing Committee on Constitution and By-Laws.

ACKNOWLEDGMENTS: Your executive secretary wishes to express his sincere appreciation to our president, Dr. P. H. Woutat, and those other splendid gentlemen for their efforts in behalf of this association. My heartfelt thanks to all with whom this writer has had occasion to work during this past year in the association's program of public enlightenment to the great problems of medicine and of its efforts to bring ever-improving medical services to the people of North Dakota.

LYLE A. LIMOND, Executive Secretary

TREASURER'S REPORT

Dr. E. I. Larson, Treasurer

Schedule of Cash Receipts and Disbursements for the Period from March 31, 1954 to March 31, 1955

Balance on hand March 31, 1954, First James River National Bank		$24,455.08
Receipts:		
Dues	$27,517.50	
Interest on U. S. Government Bonds	115.75	
Total Receipts		27,633.25
Total Cash		$52,088.33
Disbursements		
Vouchers No. 254 to No. 270 inclusive		
Checks No. 657 to No. 674 inclusive		
4-14-54 S. E. Holaday, CPA, treasurer's audit		$ 20.00
4-24-54 Mrs. A. A. Nichols, refund one-half year's dues		25.00
5-11-54 Mrs. A. A. Nichols, refund balance dues		25.00
5-18-54 Student, A.M.A. University of North Dakota, travel expense		100.00
5-18-54 School of Medicine, University of North Dakota, scholarship prizes		500.00
6-12-54 Executive Secretary, state association, one-quarter yearly budget		4,000.00
7-7-54 Dr. W. A. Wright, expense, A.M.A. meeting		340.29
7-14-54 Newberry Insurance Agency, treasurer's bond		25.00
8-25-54 Executive Secretary state association, one-quarter yearly budget		4,000.00
10-18-54 E. J. Larson, Treasurer, processing government bonds		2.50
11-2-54 THE JOURNAL-LANCET, subscriptions		758.00
11-23-54 Executive Secretary state association, deficit 1954 meeting		155.82
12-3-54 Executive Secretary state association, one-quarter yearly budget		4,000.00
12-18-54 Dr. W. A. Wright, expense, A.M.A., Miami		319.30
1-5-55 Executive Secretary state association, pre-convention expense		1,000.00
2-22-55 Executive Secretary state association, balance budget 1954-55		4,540.00
3-24-55 Executive Secretary state association, public policy and legislation		1,051.91
3-31-55 First James River National Bank, bank charges for year		.20
Total Expenditures		$20,863.02
3-31-55 Balance on deposit, First James River National Bank		$31,225.31
Other Fund Assets:		
U. S. Government Bonds		4,500.00
Total Fund Assets		$35,725.31

SCHEDULE OF U. S. GOVERNMENT BONDS
March 31, 1955

Series	*Number*	*Date issued*	*Date due*	*Issue price*
G	M1576326-G	July 1953	July 1955	$1,000.00
G	M1576327-G	July 1953	July 1955	1,000.00
K	D137110-K	Sept. 29, 1954	Sept. 29, 1966	500.00
K	D137111-K	Sept. 29, 1954	Sept. 29, 1966	500.00
K	D137112-K	Sept. 29, 1954	Sept. 29, 1966	500.00
K	D137113-K	Sept. 29, 1954	Sept. 29, 1966	500.00
K	D137114-K	Sept. 29, 1954	Sept. 29, 1966	500.00
			Total	$4,500.00

Series G bonds number D280761-G, D280762-G, D280763-G, D280759-G, and D280760-G, which matured in July 1954 were cashed and bonds number D137110-K, D137111-K, D137112-K, D137113-K, and D137114-K were purchased to replace them.

Dr. Sandmeyer moved that the reading of the reports of the chairman of the council, councillors, and special committees be dispensed with and referred to reference committee number 2. This motion was seconded by Dr. Vandergon and carried.

Report of the Chairman of the Council

1954-1955

Regular meetings were held on May 1 and May 2, 1954 at the annual meeting of the North Dakota State Medical Association. All members were present including a number of ex-officio officers. The budget for the coming year was drawn up.

In adopting the budget, there was considerable discussion on whether or not to pay the expenses of the alternate delegate to the American Medical Association meetings, and it was voted not to allow such expenses. An expense account is to be allowed to the official delegate and to the executive secretary.

There was a discussion on raising the dues of the state association to $75 in order to balance the budget and keep from having a deficit each year. A motion favoring this raise in dues was passed and presented to the House of Delegates. A resolution was adopted approving consideration of the House of Delegates against Senate Bill 3114 and HR Bill 8356 covering President Eisenhower's "reinsurance program." The Journal-Lancet was continued for another year as the official magazine of this society.

There was considerable discussion concerning a recommendation from the House of Delegates that money in the sinking fund of approximately $20,000 be better invested from a standpoint of a higher rate of interest. After a lengthy discussion, it was decided by the Council that this amount must be carried in the treasury to meet any possible emergency, and that the maximum which could be invested would be only the $4,500 that is now in government bonds. Inasmuch as most of these come due in 1954-55, it was moved, seconded and carried that the maturing bonds should be left intact to draw a higher rate of interest than they are at the present time, and also leave the money for rapid availability in case it is needed.

The motion was carried that the Mixer for doctors, nurses, guests and exhibitors held on Sunday evening during the State Convention should be continued as a convention expense.

Officers were elected for the coming year as follows: Dr. J. C. Fawcett, chairman; Dr. Amos Gilsdorf, vice-chairman; Dr. R. D. Nierling, secretary.

Dr. Nierling and Dr. Radl were to serve with the chairman as an executive committee.

A special interim meeting of the Council was held at the Dacotah Hotel in Grand Forks on July 9, 1954.

The motion was carried that a pre-convention fund of $1,000 be set up for the annual meeting of the North Dakota State Medical Association.

It was also decided that the North Dakota State Medical Association cooperate with the State Department of Health in buying and distributing pamphlets put out by the World Health Organization entitled "Medical Certification of Death." These are to be used by physicians in guidance in filling out death certificates.

An excellent presentation was made concerning the status of medical education in North Dakota by Dr. T. H. Harwood, dean, School of Medicine, University of North Dakota. In this he outlined the steps necessary in the sound development of the third and fourth years at our present two-year school of medicine. Acceptance of these proposals as outlined by Dr. Harwood was passed unanimously by the Council. The Council further assured Dean Harwood of its sincere interest in the growth and development of the School of Medicine by this acceptance of his program, and by offering him continued support.

The regular interim meeting of the Council was held at the Gardner Hotel in Fargo on December 11, 1954.

A very good representation beside the Council members were present.

A good deal of the time of this meeting was taken up with a hearing on one of our members, resulting from charges presented to the Council through the Board of Censors of his District Society. After hearing evidence and representations from the Board of Censors, and from the doctor involved, the Council decided that the physician involved was at least, in part, guilty of the various charges presented, and he was censored by the Council. It was recommended to him that he adhere to the recommendations for accreditation of small hospitals, and to the rules and regulations of their staffs.

A motion was carried that the Council approve having an organization of an affiliate of the Heart Association in North Dakota and urged persons interested to proceed with such organization, and also investigate the possibilities of the Executive Secretary helping with this organization.

The Council was advised that the physicians draft law would expire in June, but that selective service will still demand the men graduating from school, unless deferred because of residency. Availability of local practicing physicians would be determined by the local draft boards. The Council was also notified that the Veterans Medical Service of the North Dakota State Medical Association would be eliminated entirely as of the first of the year, although the same work would be carried on as direct contact between the Veterans Administration and the individual physicians.

There was a discussion of the Connecticut Pattern of incorporating medical clinics, and after receiving such information as was available from the state of Connecticut, and from the legal department of the American Medical Association, a motion was passed by the Council that any such plan be tabled indefinitely.

After discussion, it was recommended by the Council that both the Council and the House of Delegates meet in Aberdeen at the South Dakota seventy-fifth anniversary meeting in 1956, and not prior to the meeting as suggested by the House of Delegates at their meeting in Grand Forks in May 1954. It further recommended that the House take this action at their coming meeting in Bismarck on April 30 and May 1, 1955.

On June 5, 1954, I awarded medical prizes in the amount of $500 to sophomore honor students at the University Medical School as follows: anatomy, Robert J. Olson and Donald M. Yamaguchi; physiology and pharmacology, Mervin Campbell; bacteriology, Kenneth Walter Sell; pathology, Russell A. Rohde; and first year, Robert J. Olson.

John C. Fawcett, M.D., Chairman

REPORTS OF COUNCILLORS

First District

This District Society held monthly meetings in Fargo from September through April.

On April 5, 1954 the Society met with the North Dakota State Cancer Society. Dr. C. M. Lund, Williston, North Dakota, director of the State Cancer Society, introduced Dr. O. H. Beahrs of the surgical section of the Mayo Clinic, Rochester, Minnesota. Dr. Beahrs talked on "Surgical Management of Carcinoma of the Colon." Dr. J. R. Hodgson of the Radiology Department of the Mayo Clinic spoke on "Radiologic Diagnosis of Carcinoma of the Colon." Dr. Lund and Dr. Beahrs entertained the group with feats of magic at this meeting.

A special meeting of the Society was held on April 12,

1954. It was explained by Dr. B. A. Mazur, chairman of the Public Health Committee, that Cass County had been chosen as a location for trial of the Salk poliomyelitis vaccine. After discussion as to the safety of the vaccine and other features, it was moved that the First District Medical Society endorse the trial of poliomyelitis vaccination on the basis of information that the vaccine has been safely used. At the regular April meeting, Dr. Mazur reported on the progress of the polio immunization program and asked for help from members of the Society for the administration of the vaccine. At this meeting the matter of participation in the Blue Shield-Blue Cross insurance program was discussed at some length. After considerable discussion a motion was passed that the Society go on record as favoring the continuation of the Blue Shield program. A number of questions in regard to Blue Cross-Blue Shield were raised by members of the Society. Mr. Donald Eagles, manager of the North Dakota Blue Cross-Blue Shield, and Mr. Gene Bakke, public relations manager, answered these questions and further discussion followed.

The September 27, 1954 meeting was addressed by Dr. P. H. Woutat, president of the North Dakota State Medical Association. Dr. Woutat gave an informative report on the problems and work of the State Society and its committees. Dr. C. J. Glaspel, executive officer of the North Dakota State Board of Medical Examiners, also spoke. Dr. Glaspel presented some of the problems which the Board has in reference to licensing physicians.

At the November 4, 1954 meeting, the scientific program was presented by the North Dakota Tuberculosis and Health Association. Mr. James Swomley, executive director, spoke on the activities of the Association. He introduced Dr. Julius Wilson, medical education director of the American Trudeau Society. Dr. Wilson gave an excellent paper on "Present Day Concepts of the Treatment of Tuberculosis." At the November 29, 1954 meeting, Dr. Henry A. Norum of Fargo, North Dakota, and Dr. Imar Kiesel of Page, North Dakota, were voted to active membership in the Society. Dr. Robert Salassa from the Section of Metabolism at the Mayo Clinic, Rochester, Minnesota, spoke on "Some Aspects in the Diagnosis and Treatment of Hyperthyroidism."

At the December 27, 1954 meeting, a change in the by-laws was made. Starting in April 1955 the society will meet on the last Tuesday of each month instead of the last Monday. The following men were elected to office: Dr. Hugh Hawn, president; Dr. George Foster, vice-president; and Dr. Howard Hall, secretary-treasurer.

In January 1955 the Society voted to contribute $50 to the National Society for Medical Research. The scientific portion was presented by the Eli Lilly Research Laboratories. Dr. Kenneth G. Kohlstaedt, director of the Clinical Research Division, presented a paper on "Experience with New Drugs," particularly one which has shown promise in treatment of hypercholesterolemia.

The February meeting speaker was Dr. Edmund B. Flink, professor of medicine at the University of Minnesota and chief of the medical service at the Minneapolis Veterans Administration Hospitals. Dr. Flink gave an excellent paper on "Problems Associated with Metabolic Alkalosis."

Two members of the society died during the year: Dr. Olaf Sand and Dr. Carl Elofson.

Credit for this report should be given to our able secretary, G. Howard Hall, M.D.

O. A. Sedlak, M.D., Councillor

Second District

The Devils Lake District Medical Society had ten scheduled monthly meetings for the year 1954. At the majority of these meetings, outside speakers were present, with scientific papers. These included the annual visit of our state president, Dr. P. H. Woutat.

Our meetings have been well attended, and the enrollment of the society has remained static. We have had no friction in the society: Officers for 1955 are: president, Dr. J. Terlecki; vice-president, Dr. G. W. Seibel; secretary-treasurer, Dr. L. F. Pine; delegates, Dr. G. W. Toomey and Dr. William Fox; and alternate delegates, Dr. E. Schwinghamer and Dr. Robert Fawcett.

John C. Fawcett, M.D., Councillor

Third District

The following is the report of the councillor for the Third District.

As councillor for the Traill-Steele and Grand Forks District Medical Societies, it gives me a great deal of pleasure to report that both societies have had a very healthy and active year.

The following report was submitted to me by Dr. Syver Vinje of Hillsboro, North Dakota, secretary of the Traill-Steele Society:

Traill-Steele is one of the small medical societies of the state, but keeps up a steady membership of about ten. Steele County gives us just one member at present; the old standby, Dr. Dekker.

We have three or four meetings a year, generally held at Mayville.

At a meeting held on April 27, last spring, Dr. Nelson A. Youngs was our guest speaker. He spoke quite a bit about the work of a district councillor and gave, in addition, a comprehensive address on the subject of "headaches."

At a meeting of our society on August 31, Dr. Youngs was present, and in addition, as Specials, Dr. C. J. Glaspel of Grafton, Dr. O. A. Sedlak of Fargo and Dr. Philip Woutat of Grand Forks, who all came to get reports from various Traill-Steele members on the unethical ways or practice by a member of the Traill-Steele Society. Certain modes of action were agreed upon by those present to help bring a stop to this bad situation of unethical practice. Recent reports to me from Dr. McLean about this case indicate that the corrective work has been successful.

At a meeting of our Society on October 6, 1954, Dr. A. E. Culmer, Jr., Grand Forks, specialist in orthopedics, gave a comprehensive and instructive address on "Shoulder Troubles."

The Grand Forks District Medical Society has 67 members. Dr. Edgar Haunz of Grand Forks has been elected president for the ensuing year with Dr. Myron Talbert as secretary-treasurer.

Nine meetings were held, all of which were very well attended. High caliber scientific programs were presented.

Nelson A. Youngs, M.D., Councillor

Fourth District

The Northwest Medical Society now has a membership of 63. There are three honorary members, 1 complimentary and one member in service. The officers are: president, Dr. Roger Sorenson; vice-president, Dr. Frank Naegeli; and secretary-treasurer, Dr. William Kitto. Delegates to the State Society are: Dr. A. R. Sorenson, Dr. G. M. Hart, Dr. A. F. Hammargren, Dr. Fred Erenfeld, and Dr. V. J. Fischer. Alternates are: Dr. Oliver Uthus, Dr. Henry Kermott, Dr. Martin Conroy, Dr. W. B. Huntley, and Dr. J. L. Devine. Board of Censors are: Dr. G. S. Seiffert, Dr. Fred Erenfeld, and Dr. M. W. Garrison.

We have held 9 regular meetings during the year, alternating between the two hospitals, St. Joseph's and Trinity.

The speakers at the meetings were: Dr. W. Robert Schmidt, Minneapolis, "Surgery and Cardiovascular Lesions"; Dr. W. L. Macauley, Fargo, "Recent Advances in Dermatology"; Dr. Jack Friedman and Dr. Lyle J. Hay discussed X-ray Diagnosis of Cancer of the Colon and Surgical Treatment of Carcinoma of the Colon; Dr. T. H. Harwood, dean of the University of North Dakota Medical School, Grand Forks, discussed Contemporary Problems in Medical Education; Dr. John Freeman, Jamestown, discussed Care of Mental Patients in the State of North Dakota; Dr. Douglas, Mayo Clinic, presented a discussion of the North Dakota Tuberculosis Association; motion pictures on the training of medical technologists presented; and Dr. Lee Christoferson, Fargo, "Congenital Vascular Anomalies of the Central Nervous System."

Kotana District

The Kotana Medical Society elected officers on February 26, 1954 as follows: president, Dr. C. M. Lund; vice-president, Dr. F. Blankstein; and secretary-treasurer, Dr. D. E. Skjei.

Four meetings were held during the year: January, Dr. J. J. Ayash, Minot, discussed Vertigo. This was also a business meeting; March, talks by cancer group; and June, Dr. Lee Christoferson, Fargo, discussed Hydrocephalus. This meeting was held in Crosby.

The Kotana District Medical Society has a membership of 16.

A. D. McCannel, M.D., Councillor

Fifth District

The Sheyenne Valley Medical Society held 7 meetings during the year. This was a decided improvement over the previous year. One of the most interesting meetings was the Cancer Caravan held in April, when Drs. Hodgson and Beaher spoke on "Carcinoma of the Colon."

A blood bank was held in August. This was preceded by a demonstration of blood-letting on the local TV station sponsored by the Society. The bank was fairly successful.

Another very informative and timely program was held in November when Dr. Melton of Fargo presented a series of his own cases and gave a good synopsis of present day treatment and management of skin lesions.

We have not progressed too far in getting a regular monthly meeting, but are trying to make arrangements to have monthly clinical pathology conferences.

W. H. Gilsdorf, M.D., Councillor

Sixth District

Five meetings of this society were held during the year of 1954 with an average attendance of 44. The membership at the end of the year was 69.

Officers for 1955 are as follows: president, Dr. Robert F. Nuessle, Bismarck; vice-president, Dr. Ralph Vinje, Bismarck; and secretary-treasurer, Dr. Robert Kling, Bismarck. Delegates are: Drs. M. S. Jacobson, Elgin; R. O. Saxvik, Jamestown; C. H. Peters, Bismarck; C. J. Baumgartner, Bismarck; and O. C. Gaebe, New Salem. Board of Censors are: Dr. E. D. Perrin, Bismarck; R. W. Henderson, Bismarck; and G. R. Lipp, Bismarck.

The guest speaker at the first meeting was Dr. Olaf Gardebring, consultant psychologist with the North Dakota State Mental Health Committee. He spoke on psychosomatic medicine. The next meeting was one sponsored by the North Dakota State Cancer Society. The guest speakers were Drs. Burrs and Hodgson of the Mayo Clinic, Rochester, Minnesota, their subject being "Carcinoma of the Colon." Dr. Parris of the National Poliomyelitis Foundation also spoke on polio vaccines. At the next meeting Dr. Roger M. Berg spoke on "Radioactive Isotopes in Common Clinical Use." The next meeting was sponsored by the North Dakota Tuberculosis and Health Association. The speaker was Dr. Julius L. Wilson, professor of medicine of the University of Pennsylvania Medical School. His subject was Modern Concepts in the Treatment of Tuberculosis." Dr. Robert B. Tudor of Bismarck spoke at the last meeting, the subject being "Sudden Deaths in Infants."

Members who joined the Sixth District Society in 1954 are: Dr. E. J. Mears, Bismarck; and Dr. Erie Walter, Bismarck.

Dr. Zoya Kudinoff, of Halliday, and Dr. J. M. Bahamonde, of Elgin, transferred out of the society as they had left the state of North Dakota.

Robert B. Radl, M.D., Councillor

Seventh District

Since the annual meeting of the State Association in May 1954 the Stutsman County Medical Society has had 5 meetings. On Thursday, May 27, 1954, a dinner meeting was held at the Jamestown Hospital. A committee of Dr. E. J. Larson, as chairman, and Drs. Elsworth and Van der Linde was appointed by President Dr. McFadden to study and recommend any changes in the fee schedule of the North Dakota Physicians Service; this report to be rendered to the latter not later than June 15. Three medical students from the University of North Dakota, here on a preceptorship, Walter Eidbo, Mervin Campbell and Leonard Linde, were guests.

Dr. C. J. Glaspel of Grafton, secretary of the State Board of Medical Examiners, spoke to the group on the subject of Medical Licensure and the problems related thereto. His talk revolved around four subjects: revocation of licenses; chiropractors and osteopaths; foreign medical graduates, and American students in substandard European medical schools.

The second meeting was held Thursday, October 7, 1954, at the Jamestown Hospital. Dr. Robert Kooiker was voted into the Society as an active member. Dr. Kooiker is practicing at the State Hospital in Jamestown.

Dr. Dale H. Correa of Minneapolis read a paper on the subject of "Pheochromocytoma." He also showed a few slides showing various aspects of the disease. Dr. Gordon Strom, also of Minneapolis, followed with a discussion of "Surgery of the Adrenal Gland," methods of approach, pathology, etc., and he also had a few slides illustrating the various points of his subject.

The third meeting was held on Monday, November 8, 1954, at the Moline Cafe. Mr. Edward Sypnieski, North Dakota Field Representative of the Tuberculosis and Health Association was introduced by Dr. McFadden. Mr. Sypnieski outlined a plan whereby the Association is to sponsor a guest speaker each year and to bring this man, an M.D., to each County Society for a paper upon some phase of tuberculosis. He introduced this year's representative, Dr. Bruce Douglass, who is in the Internal Medicine Department of the Mayo Clinic. Dr. Douglass gave a very interesting talk on the subject of "Recent Trends in the Treatment of Pulmonary Tuberculosis," and illustrated some of his points with slides. The trend, as pointed out by Dr. Douglass, is toward lengthy treatment with the antibiotics, usually streptomycin, isonicotinic acid and P.A.S.

The fourth meeting was held on Thursday, January 27, 1955, at the Jamestown Hospital. Officers for the year 1955 were elected: president, Dr. John A. Beall; vice-president, Dr. Neville Turner; and secretary-treasurer, Dr. R. D. Nierling. Delegates are: Dr. Thomas E. Pederson and Dr. John Van der Linde. Alternate delegate: Dr. John N. Elsworth. Censors are: 3 year, Dr. George

Holt; 2 year, Dr. John Van der Linde; and 1 year, Dr. Ellis Oster.

Dr. E. J. Larson presented a resolution to the Society as follows: "Resolved that the Stutsman County Medical Society is able and willing to assist the North Dakota State Hospital in several fields of medical practice and the State Hospital should be informed of the medical and surgical facilities available in Jamestown. It is the opinion of our Society that much money can be saved by making full use of the facilities already here. It is also resolved that Dr. John Elsworth is authorized to present the facts to Dr. Russell Saxvik, superintendent of the State Hospital."

Considerable discussion of the Resolution followed and it was passed as above worded.

A film "Post Mortem Tissue Donation," depicting the preservation and storage of bodily tissues following death, was shown. This film was prepared by the Naval Medical Center and the National Morticians Association. Following this, two reels of a film of an original telecast entitled "The Management of Hypertension" was viewed. The panel of four prominent physicians, moderated by Dr. Cyrus C. Sturgis, president of the American College of Physicians, consisted of Dr. F. H. Smirk of New Zealand, Dr. Edward Freis of Georgetown University and adjunct professor of medicine at Boston University, and Dr. Garfield G. Duncan, professor of medicine at Jefferson Medical College in Philadelphia. The film dealt largely with the newer ganglionic blocking agents.

A meeting of the Society was held Thursday, March 3, 1955, at the Jamestown Hospital. Dr. John Young of the State Hospital, Dr. Samuel Miller, radiologist at the DePuy-Sorkness Clinic, and Richard Steidl, M.D. of Kulm were voted into membership in the Society.

Flowers were sent to Dr. W. Gerrish's funeral at Alhambra, California, and a note of appreciation from his wife was read to the Society by the secretary.

Dr. Lee Christoferson of Fargo gave an interesting talk upon the subject "Spontaneous Subarachnoid Hemorrhage, the Diagnosis and Treatment." He illustrated some of the cases by angiogram slides. Dr. Christoferson answered many questions following his paper.

The Annual Cancer Caravan, with its speakers and Dr. Caroll Lund, will visit Jamestown on Wednesday, March 30, 1955.

R. D. Nierling, M.D., Councillor

Ninth District

The Southwest District Medical Society had 5 official meetings in 1954, all of which were held at Dickinson, North Dakota.

The first regular meeting was February 13, 1954, as a dinner meeting at the Ray Hotel followed by a scientific meeting. Dr. Ralph Vinje and Mr. R. J. Sailer of the North Dakota Workmen's Compensation Bureau were guests. The first part of the meeting was taken up with discussion of the relationship between the North Dakota Compensation Bureau and patient management, claims, disability, etc. Following this, a scientific paper was given by Dr. Ralph Vinje on the management of severe trauma.

The next regular meeting was held on June 12, 1954. Dr. Robert Gilliland gave a report regarding the Blue Cross-Blue Shield meeting in Grand Forks at the spring state medical meeting. Dr. Rodgers discussed possible changes in a new Blue Shield plan. All members of the society were given the opportunity to sutdy the present Blue Shield schedule and forward their recommendations for changes to the Blue Shield-Blue Cross representatives of our society. Dr. A. R. Gilsdorf gave a report on his meeting in Omaha in regard to veterans' medical care. The members of the society were also informed as to the necessity for increasing the state medical dues to balance our budget. Dr. R. W. Rodgers reported on his activities as delegate in the spring state society meeting.

The next regular meeting was held October 9, 1954, which again was a dinner meeting. Dr. Warren L. Macaulay of Fargo, North Dakota, was guest speaker. His topic was "Skin Diseases of Interest to the General Practitioner."

The fourth regular district society meeting was held November 9, 1954. The guest speaker was Dr. Warren Douglass of the Mayo Clinic. His topic was "The Modern Concepts of Tubercular Therapy," and it was presented at St. Joseph's Hospital, Dickinson, North Dakota. After the scientific paper was presented, individual cases were presented for open consultation.

The fifth and final meeting of the year was held December 11, 1954. This was essentially a business meeting. The following officers were elected for 1955: president, Keith Foster, M.D.; vice-president, Ralph J. Dukart, M.D.; and secretary-treasurer, H. L. Reichert, M.D. Delegates to State Meeting are: R. F. Gilliland, M.D., and Keith Foster, M.D. Alternates are: John W. Denser, M.D., and Julian Tosky, M.D. Councillors are: A. J. Gumper, M.D., A. A. Curiskis, M.D., and James J. Moses, M.D.

A motion was made to accept the application of Dr. William M. Buckingham for transfer from the Sixth District to the Ninth District. This was voted upon and accepted by the society. A program committee for the district was appointed with the following membership: Dr. Robert Gilliland, Dr. Keith Foster, and Dr. A. R. Gilsdorf.

The Southwest District now has 23 regular, active members and 5 retired members. We lost 2 members by transfer to other states; Dr. John H. McNeil, previously of Hettinger, North Dakota, and Dr. Ralph Gustin, formerly of Beach, North Dakota. We have gained Dr. William Buckingham of Elgin, a transfer from the Sixth District to our district and Gladys Martin, M.D., pediatrician of Dickinson, North Dakota.

A. R. Gilsdorf, M.D., Councillor

SPECIAL COMMITTEES

Committee on Emergency Medical Service

During the past year a survey has been conducted concerning the Emergency Medical Services in the following states: Wisconsin, Minnesota, South Dakota, Colorado, Wyoming, Montana, Washington, and Idaho. South Dakota and Montana did not respond to the questionnaire, but all of the others sent full details concerning their respective plans The undersigned also visited state medical association offices in Idaho, Oregon, Minnesota, Wisconsin, and Illinois and discussed emergency medical service committee functions as understood in those states.

It appears that North Dakota is far behind the rest of the central and northwestern parts of the nation in regard to emergency medical services. In all of the states visited, and in those from whom detailed data was received, state civil defense agencies had taken over development of facilities for emergency medical services in case of military action, and in most instances the same organization also functioned in event of natural disaster. The author was told repeatedly that while a committee of a medical association might formulate paper plans for emergency service, it could not solve the problems of transportation, communication, supply, nursing, allied

services, and public health. The result is that everywhere state medical associations have joined with the civil defense agencies in preparing written plans supplying emergency medical services. In most instances, civil defense officials have taken the initiative and have asked state medical associations to furnish planning committees, together with advisory committees including representatives of organized nursing, pharmacy, public health agencies, transportation, and supply agencies and so on. However, in North Dakota there seems to be comparatively little interest in civil defense, and no written medical plan exists. If such a plan is to be developed, then the initiative must apparently be taken by organized medicine in this state.

Detailed plans for medical services by the Federal Civil Defense Agency were formulated and distributed a number of years ago. Virtually all states use the federal plan or a modification of it. In general, two types of modifications occur: a) when state population is predominantly urban and industrial, as in Michigan; and b) when state population is mostly rural and agricultural, as in Idaho The basic organization at the state level is the same in all states studied, the modification having been made by state medical association committees and the advisory committees of the allied professions. A summary of the various existing plans studied is given below:

A. The Idaho Plan. Under the state director of civil defense there is an assistant director of health services, and, under him, four chiefs of divisions covering medical services, public health services, veterinary services and radiological services. The state is divided into six regions for emergency medical service purposes, each headed by a physician and two assistants. In each region, mobile first aid teams and mobile medical-hospital teams have been organized and trained. These can be transported anywhere in the state. Medical and hospital facilities have been inventoried, and some stockpiling of non-perishable medical and hospital supplies has been accomplished. The plan recognized the fact that the population is sparse and widely scattered and that no one region could take care of its own needs; hence, emphasis on mobile units. The other divisions are also well organized and their function dovetails wtih those of medical services. The plan will operate in both natural disasters and in case of military attack.

B. The Wyoming Plan. At the state level, the plan follows that given in Federal Civil Defense Technical Manual 11-1, and local plans are on a county-city basis. There is a medical services branch, comprising first aid and ambulance service, hospitals, casualty treatment and evacuation, general medical care, pediatric and obstetric care, mental health, dental care, pharmacy, and nursing care. Other branches cover public health services, special weapons defense, health supplies, sanitation supplies and mortuary supplies. Because of sparsity of population and vast areas, much leeway is allowed in the various county organizations, but Dr. Drew tells us that most communities and counties are now organized and at least partially trained.

C. The Colorado Plan. At the state level the federal plans are used, but at local levels great emphasis has been placed on hospitalization plans. Existing hospitals, auxiliary hospitals and improvised hospitals are all provided for in such detail that the plans cannot be quoted here, as they include standing medication orders and many other details. With this, elaborate first aid and evacuation systems have also been developed. We are informed that all existing hospitals have their own disaster plans, again in minute detail. The plans would be used in event of natural disaster and other catastrophies as well as in event of military attack.

D. The Washington Plan. This very elaborate and detailed plan was submitted to us as a large mimeographed manual. It follows the general Federal Civil Defense Technical Manual in general, but is much modified. The state is divided into 9 areas, corresponding with public health districts. Much legislation has been accomplished to implement disaster planning, and particular emphasis has been placed on mobile support, in the form of "mobile support units," and "mobile support teams." Development of such teams, with provision for supply of personnel and their transportation to any portion of the state, seems to dominate this plan. Disaster hospitalization plans are much less developed than in some states, but much emphasis has been placed on the role of state and local public health agencies and of the place of the American Red Cross in event of disaster or attack.

E. The Oregon Plan. Following the general federal plans, responsibility is placed on individual counties to provide "mobile first aid teams" and "mobile emergency medical-hospital teams." These may be transported to any portion of the state or to any adjoining state in event of disaster or attack. Their movement and utilization is controlled by the state civil defense agency. There are 13 counties which do not have "mobile emergency medical-hospital teams" because of insufficient personnel, but are covered by adjoining counties. The plan is comparatively simple and especially adapted to a state in which there are a number of sizable cities, and a sparse rural population.

The heart of the medical service plan is the "emergency medical-hospital team." It is composed of the following (to serve 300 beds): 8 physicians, 4 dentists, 15 registered nurses, 25 nurse's aids (female), 10 nurse's aids or orderlies (male), 2 pharmacists, 4 laboratory technologists, and 9 mortuary personnel, including coroner and clerks.

Additional non-professional personnel (cooks, janitors, drivers, stretcher-bearers, etc.) are provided by local defense deputies.

Standing orders for nurses, nurses' activities, plans for public health activities, and a myriad of other duties and functions are detailed.

Also detailed plans for procurement of blood have been provided, the work of someone experienced in blood banking. "Bleeding teams" are composed of 2 physicians, 6 to 8 nurses, 1 technologist, 1 blood custodian, and 16 to 20 lay volunteers. Every county must train at least 1 bleeding team per 20,000 population, and every community must have at least 1 bleeding team with each blood bank or hopsital transfusion service, regardless of population. This is one of the best plans seen and adaptable in its entirety to our own state.

F. The Minnesota Plan. This plan is chiefly designed to provide evacuation of the larger cities in event of disaster, but can be adapted to smaller communities. Casualties from Minneapolis and St. Paul, for example, would be first attended by mobile first aid teams. Twenty of these teams are now fully trained and equipped. After first aid has been accomplished, casualties would be evacuated to medical evacuation centers in communities adjacent to the cities, thence to one of 53 definitive hospital points in southern Minnesota. Those from Duluth would go to one of 25 definitive hospital points in northern Minnesota. We are told that 50 per cent of such hospital points are now operational. There are some phases of this greatly detailed plan that might be applicable to our own situation, but it is primarily de-

signed for a highly concentrated urban population, and mainly for use in military attack, though it could be used in event of a tornado or other natural disaster.

G. The Michigan Plan. This is designed mainly for care and evacuation of populations of industrial cities, utilizing public health personnel in authoritative positions more than in other states. The plan is new, just coming off the press, and parts of it are not yet available. First aid, evacuation, and definitive treatment plans are given in much detail, and a particularly elaborate "blood collection manual" has also been prepared. This provides for collection of very large quantities of whole blood and anticipates huge casualties in the cities. It is primarily designed for use in military attack.

H. The Wisconsin Plan. Again organized within the framework of civil defense, the plan was developed through the combined efforts of civil defense medical department personnel, a committee of the state medical association, and an advisory committee representing hospital administrators, state department of agriculture, pharmacists, public health workers, nurses, dentists, the American Red Cross, veterinarians, and funeral directors.

The plan provides for division of the state into 8 areas, with a medical director for each, and the basic unit is the "medical team," consisting of 2 physicians, 2 dentists, 2 nurses, and a variety of non-professional personnel; 29 persons in all. The number of teams in a given area is governed by the population. There are elaborate plans for first aid and evacuation, and the "medical teams," fully mobile, move into, or adjacent to, disaster areas and establish casualty stations. These prepare casualties for further evacuation to hospitals. The set-up resembles the numbered collecting stations of World War II.

The North Dakota Situation

It appears that there is no existing written medical emergency plan for this state. Correspondence with officials of the above states indicates that in their opinion no effective emergency medical service can be developed by medical personnel alone. It must have the backing and authority of an agency at the state governmental level, and for this reason all of these states have cooperated with their respective state civil defense agencies, previous emergency plans have been discarded as unworkable. Furthermore, the problems of supply, transportation, communication, procurement of lay helpers, and innumerable others cannot be solved by physicians who, in event of disaster, must spend their energies in the care of casualties. Physicians are used to handling emergencies on a small scale, but not on the scale seen in either natural disaster or military attack.

There are not as many doctors and nurses in the entire state of North Dakota as there are in many of the cities of states whose plans have been briefly described here. Our population is sparse and scattered over wide areas. Any plan workable here must be based on mobility of organized units, these moving into disaster areas upon direction by higher authority, preferably at state level. Such units must include medical and nursing personnel, first aid workers, and the great variety of lay and professional workers needed to supplement and support those specifically charged with the care of the injured.

The best way, and possibly the only effective way, of developing such an emergency medical service is through a strong civil defense agency. If this agency can be induced to take the lead, then committees of the state medical association, together with public health personnel and represntatives from the allied professions, can aid in developing such plans. There is a plan already in existence which could be used with little modification, that of the state of Oregon.

Formation of a blood bank committee, appointed from the state medical society, is also needed. In event an emergency medical plan can be formulated under the civil defense agency, such a committee would be charged with formation of a blood procurement plan. Even without this there are certain problems in blood banking now affecting every physician and every hospital that should be considered and dealt with by such a committee. These include development of standards in blood banking, standards for donors, development of rules for replacements, equalization of charges and replacement requirements, standards for blood bank personnel, and many others.

It is recommended:

1. That the North Dakota State Medical Association request the director of civil defense to form a written plan for emergency medical service, operative in natural disasters and in event of military attack.

2. That this plan be developed by medical representatives from the state civil defense agency, and a committee appointed by the North Dakota State Medical Society.

3. Further, that an advisory committee representing hospital administrators, nursing groups, dentists, state public health personnel, pharmacists, veterinarians, American Red Cross, and other allied professions, be formed to aid the civil defense agency and the state medical association in preparation of such a plan.

4. That this plan follow, in general, that proposed by the Federal Civil Defense Agency, modified to meet our peculiar requirements regarding population and geography; and,

5. That a blood bank committee be appointed by the state medical association to cooperate with the civil defense agency in forming a plan for blood procurement in event of disaster, and to study the special problems of blood banking in this state.

John D. LeMar, M.D., Chairman

Committee on American Medical Education Foundation

It is a pleasure to be able to report a decided increase in the donations throughout the state to the American Medical Education Foundation. The number of contributors has increased from 13 two years ago, to 60 in 1954, and the donations have reached a high of $2,600.

In order to bear the burden more equitably, two states—Illinois and Utah—have raised their donations through assessments of $20 per member. Illinois' 8,837 members raised $185,095.68 and Utah, with 535 members, raised $11,090. All the Illinois members are not happy because some think their state is bearing an undue burden; comparing it with other states, I believe so, too. People hate being told how much to give or even that they have to give. Voluntary gifts from men who believe in what they are supporting are what we want. At the present rate of increase our present total should soon be doubled.

Our own University of North Dakota has received a total of $36,177.50 through this program. The national fund this year has for the first time produced more than the medical profession.

We must not forget the use of memorials. The women's auxiliaries have raised a total of $45,031.59 in 1954—$10,311.35 of this amount as memorial gifts. The women have been extremely active and have raised money by putting on dances, bridge parties, style shows and even knitting dish rags.

May I again urge you to give to your college through the American Medical Education Foundation.

W. E. G. Lancaster, M.D., Chairman

Committee on Diabetes

The members of the Committee are as follows: E. A. Haunz, chairman, Grand Forks; T. E. Pederson, Jamestown; Martin Hochhauser, Garrison; Lester Wold, Fargo; P. Roy Gregware, Bismarck; H. A. LaFleur, Mayville; A. K. Johnson, Williston; R. M. Fawcett, Devils Lake; W. H. Gilsdorf, Valley City; and R. F. Gilliland, Dickinson.

The function of this committee again this year was the organization of the annual diabetes detection drive as part of "National Diabetes Week" in cooperation with the American Diabetes Association and the North Dakota Diabetes Association. This was held in December.

According to established policy, each district medical society was asked to vote for or against having its own local detection drive. This year only four communities participated in the drive, resuling in a total of 1,525 tests: Bismarck, 310; Devils Lake, 79; Williston, 436; and Grand Forks, 700.

There were 69 positive urine tests in the grand total. The new Drey-Pak method of urine testing was utilized in 1010 tests, while the remaining 515 tests were performed by Clinitest. Final reports of the actual number of new diabetics discovered have not been obtained, but at least 10 cases were established in preliminary reports.

It is possible that a considerable free supply of Drey-Pak may be available for next year's drive through the American Diabetes Association. With materials available it is a simple task to test thousands of individuals at little or no expense. Lay groups such as service clubs, Jaycees, etc., are usually more than willing to cooperate with medical groups in conducting successful detection drives.

Nationwide interest in diabetes detection is growing every year. In 1954, over 700 local medical societies held detection drives. Many communities look forward to the annual drive and have become successfully educated to the fact that an annual test for diabetes is a sound public health measure. Indeed it is one of the few public health measures for which the public has never been approached for funds.

The importance of diabetes detection is not only emphasized by the million unknown cases existing in the country but even more self-evident from the statement of the Metropolitan Life Insurance Company that the number of diabetics will have increased 74 per cent while the general population will have increased only 22 per cent in the period 1940-1985, regardless of what we can do at the present level of medical science.

E. A. Haunz, M.D., Chairman

Committee on Displaced Physicians

Your committee has had 2 meetings during the past year, all members being present.

The displaced physicians program, which was established by action of the board of medical examiners in January 1949, was terminated by the same board in 1952. During this period, 22 displaced physicians were processed and permitted to write the examinations for medical license. Of this number, 15 passed and were issued a restricted license, and 7 failed. Of the 15 who passed, 1 has left the state due to her inability to cope with the professional and financial problems associated with general practice, and the remaining 14 are still in active practice. (One of these has had some difficulty with the Narcotic Bureau.)

One of these men has completed 5 years of practice, is now a United States citizen and has been re-examined by the medical board and granted an unrestricted license. Three more will be due to appear before the board this year, 7 in 1956, and 3 in 1957, at which time the program is terminated.

Your committe heartily approves the recommendation of Dr. O. A. Sedlak, chairman of the committee until this year, that the committee should continue and remain active until the last displaced physician has been processed. Your committee would welcome reports, either favorable or unfavorable, from any doctor or hospital in the state, as to the type of medical service, ethics, and behavior in general of any of these doctors.

Your committee feels that the large number of foreign physicians who are now in the United States and the large numbers due to arrive in the next few years is the greatest problem which faces each state medical association and medical licensing board. There are over 500 foreign medical schools. The A.M.A. is unable to conduct any survey or appraisal of any of these schools and indeed there is some question as to whether it would improve our international relations. There is considerable proof that none of these schools are of the high standard of United States and Canadian medical schools.

While it is the desire of this committee to act fairly and humanely to all foreign graduates, at the same time we, and the board of medical examiners, have a grave responsibility in the selection and licensure of persons who seek to practice medicine in the United States. It is our belief that statesmanship in this problem requires an attitude of tolerance and discrimination to provide a plan fair to graduates of United States medical schools and to carefully selected competent foreign graduates as well as to exclude those who are unfit.

C. J. Glaspel, M.D., Chairman

Committee on Mental Health

The meeting of the Committee was called to order at 11:45 A.M. on November 4, 1954, by the Chairman, Dr. R. O. Saxvik. Members present were: Russell O. Saxvik, M.D., John T. Cartwright, M.D., L. H. Kermott, Jr., M.D., John G. Freeman, M.D., M. J. Geib, M.D., and Lyle A. Limond, Executive Secretary, North Dakota State Medical Association.

Discussion of old business was carried on and dealt with the report of this committee to the house of delegates at the Grand Forks meeting of the North Dakota State Medical Association on May 3 and 4, 1954. This report is found on pages 76 and 77 of the 1954 Handbook of the House of Delegates.

1. The role of the State Hospital in its educational program to the North Dakota State Medical Association. (a) Educational program thus far has been that of contact with individual physicians, (b) State Hospital willing to send speakers from its medical staff to the district medical societies, (c) Need for further education regarding situation at the State Hospital, in that said hospital is not like the typical community hospital with private rooms, etc., and, (d) All physicians are to receive again copies of the Voluntary Admissions Act, plus the recommended changes (amendments being considered by the current legislative assembly).

2. Support from the North Dakota State Medical Association needed in establishing new mental health laws. (a) Need for change in commitments from criminal action into the realm of medicine. This need is to be surveyed and findings presented for approval or disapproval of the thirty-fifth Legislative Assembly in 1957, (b) Need for a law permitting 2 physicians to commit

a patient for thirty days for observation, care and treatment, (c) Need for a law on voluntary admissions changing the three-day notification of departure of patient to some longer period, like seven to ten days. The individual should also be taken in whether unable to pay or unwilling to pay at per diem rates. There is continuing money difficulties with voluntary admissions. Guarantees can easily be given the counties that the patients will not be kept at the state hospital needlessly, and (d) Need for an amendment of the law appointing the superintendent only on two-year basis. Should change term to four years.

3. In regard to the two recommendations presented to the house of delegates in May 1954, the following statements were made by the Committee: (a) Recommendation No. I. (Follow-up progress to be instituted by the state hosiptal in which the local physician caring for the discharged patient is to report to the state hospital on the patient's progress. This is part of a long-term program, and is still very difficult to institute.) The state hospital started in June 1954 to inform the hometown physician as to the discharged patient's progress to date and what was done while in the hospital, and (b) Recommendation No. II. (Efforts should be made by the state hospital to set up a residency program as soon as possible.) This can possibly be carried out by February 1956. Needs approval from the Joint Commission on Accreditation of the A.M.A. and the A.H.A. (Request has been made for survey, but most possibly will not be completed by November 1955.

Under new business, the following points were discussed:

1. Out-patient clinics in the larger cities of the state now very doubtful.

2. Vocational rehabilitation program of the Federal Government envisions the states helping meet the apparent needs in the fields of the mentally ill and the alcoholic.

3. Next meeting of the committee to be in Grafton after adjournment of the Thirty-fourth Assembly.

R. O. Saxvik, M.D., Chairman

Pharmaceutical Liaison Committee Report

In accordance with the instructions of the Thirty-third Assembly of the House of Delegates, the society president appointed a special liaison committee of the North Dakota State Medical Association to meet with the North Dakota Pharmaceutical Association at such time as the latter organization should designate. Members of the committee appointed were: Drs. M. S. Jacobson, R. D. Nierling, C. H. Peters and G. A. Dodds.

One meeting of the committee was held during 1954, on December 12th, in the Gardner Hotel, Fargo. At this meeting, Dr. P. H. Woutat acted as temporary chairman. Other state association members present were: Drs. A. C. Fortney, O. A. Sedlak, W. E. G. Lancaster, Nelson A. Youngs, T. E. Pederson, V. J. Fischer, and Mr. Lyle A. Limond. The pharmacy committee members present were: Mr. O. S. Trom of Lisbon; Mr. Al Doerr, Napoleon; Mr. Joe Halbeisen, Fargo; Mr. John Craven, Bismarck; and Dr. C. E. Miller of the North Dakota Agricultural College, Fargo. The meeting was an effort on the part of both committees to eliminate sources of irritation between the two professions. The pharmacists agreed to the correction or elimination of the following practices: counter prescribing; conversations between pharmacists and the doctor's patient regarding medication prescribed; refilling of prescriptions without the physician's approval; sale of legend drugs (drugs requiring a prescription) over the pharmacy counter; and substitution of drugs other than those specifically prescribed by a physician.

As far as the physicians were concerned, the pharmacists were found to object to two practices, namely the use of imprinted prescription blanks, and, secondly, the promiscuous dispensing of professional samples left by detail men. Your committee agrees with these objections and it is our recommendation that the House of Delegates take action to outlaw the use of imprinted prescription blanks and that each physician have his own blanks imprinted without the name of any pharmacy on the same. Secondly, the promiscuous dispensing of professional samples should be eliminated to promote better relationships with the pharmacists of the state.

The committee of pharmacists extended an invitation for someone from the North Dakota State Medical Association to be present at their next annual meeting in Minot on June 13 and 14, 1955. Inasmuch as the time of this meeting would be held after the change of officers of the state medical society, this matter is referred to the incoming society president.

G. A. Dodds, M.D., Chairman

Annual Report of the Delegate to the American Medical Association

Your delegate attended all sessions of the annual meeting of the House of Delegates of the American Medical Association at San Francisco in June and all sessions of the interim session in Miami in December. Dr. Glen Toomey, alternate delegate, attended meetings of the House of Delegates in San Francisco. I would recommend to the House of Delegates of the North Dakota State Medical Association that provision be made for defraying the expenses of the alternate delegate to attend the meetings of the House of Delegates of the American Medical Association. Many states do send their alternate delegates and the experience gained by them is of considerable value. Your delegate served as chairman of the Reference Committee on Insurance and Medical Service in Miami. Your delegate also serves as a member of the Council on Rural Health, a member of the Committee on Medical and Related Facilities of the Council on Medical Service, and is a member of the special group appointed to study methods of compensation of full-time medical teachers.

The American Medical Association is recognized as the world's leading medical scientific organization and this work is directed largely by the various councils and bureaus. The House of Delegates are primarily concerned with matters of policy and specifically policy relating to relationship between doctors, between doctors and the general public, and between doctors and the government. As you all know very well, it is necessary for doctors not only to be leaders in the scientific phases of medicine but it is vital that we play a leading role in the related social-economic fields.

As a result of constructive actions by your officers over a period of years, the A.M.A. is so organized that we may effectively present our conclusions to the general public, to our members and to legislators. Much of this educational effort is done by employees of the public relations and press departments. The Journal of the A.M.A. continues to be not only the world's leading medical journal but is a reliable source of information in the social, economic and legislative field. In the latter field we have an active legislative committee appointed by the board of trustees who review all legislation with medical implications. The Washington office has been greatly expanded. This office continues to furnish reliable information on matters of concern to medicine to legis-

lators and to the profession. In this paternalistic day of big government it is most important that medicine be able to make available to legislators and officers of the federal government some of the vast store of knowledge which is our legacy from the past and our store from the current rapid development of medical science, medicine, and medical care.

Currently the A.M.A actively supports in principle Mr. Eisenhower's recommendations for an enlarged mental illness program, the training of more nurses, a more effective rehabilitation program, a new procedure for allocating health grants, traineeships in public health, strengthening of the Public Health Service Commissioned Corps and more research in air and water pollution. The opinion that the proposed reinsurance proposals will not achieve the desired results continues to be held. At the present time, the proposals for a new arrangement for the medical care of public assistance recipients and for federal guarantee of mortgages on health facilities are being studied.

The A.M.A., through its Bureau of Medical Economic Research, continues to point out the inequities of the present social security program. Further, they are giving active support for legislation of the Jenkins-Keogh bill. This is the proposal to permit self-employed professional people to set aside retirement funds with tax-exempt funds, a privilege now being accorded industry.

The results of the last election would indicate that in the foreseeable future, one may expect more and more interest on the part of the federal government in the so-called health and welfare field. We must face the fact that these programs are popular with voters and, hence, are enthusiastically embraced by politicians and, regardless of our feeling as to their necessity or the good which may be derived from them, they are probably a permanent part of the American scene. This being the case, it is comforting to know that we are effectively organized so that we may offer advice and guidance in these programs to the end that they may work out to the best advantage of the people.

It is unfortunate that the recommendations of the medical task force regarding veterans hospital care for non-service connected disabilities were not approved by the entire Hoover Commission. The Hoover Commission recommended curtailment of such services, mainly by closing various hospitals and by examining more closely the financial status of the veterans applying for treatment of non-service connected disabilities. The medical task force has recommended that veterans be eligible for medical hospital care for non-service connected disability only for a period of three years following discharge from service. This would have greatly curtailed the extreme growth of federal medical care. The A.M.A. continues to actively oppose the extension of medical care for non-service connected disabilities.

PRE-PAYMENT INSURANCE

While the institution of pre-payment insurance has become an accepted part of the American way of life, there are still many differing opinions as to its value and the proper method of using such insurance. In an effort to try and clarify some of the thinking in the insurance field, the A.M.A. has appointed a commission to make a complete study of pre-payment insurance. The chairman of this commission is Dr. Leonard Larson, who is also a very active and valuable member of the Board of Trustees.

OSTEOPATHY

The special committee under the chairmanship of Dr. John Cline, appointed to study the osteopathic problem, will probably bring in a final report at the meeting in Atlantic City in June. At the present time, this committee is engaged in a study of the quality of teaching in osteopathic schools. It is anticipated that the report will be a reflection, to a considerable degree, of the osteopathic situation as it exists in California.

GRIEVANCE COMMITTEES

At the Miami session, a committee was appointed with Dr. J. P. Culpepper as chairman, to study the proper functioning of grievance committees.

DOCTOR DRAFT LAW

The A.M.A. has taken the position that the doctor draft law is no longer necessary and the needs of the military can be met by the regular draft and by making the service more attractive to doctors. However, it is most likely that a new doctor draft law will be presented to this session of the congress.

STATE SUBSIDIZED MEDICINE

In some states, tax-supported medical schools employ full-time medical teachers who also do private practice. In one or two of the southern states there are sufficient facilities available through tax-supported medical schools and related institutions to provide for from one-third to one-half of the entire population of the state. This entire matter is now the subject of study by a special group formed by the Council on Medical Service, the Council on Medical Education and Hospitals, the American Hospital Association and the Association of American Medical Colleges.

MALPRACTICE INSURANCE

No solution to the rising costs of malpractice insurance seems to be apparent at this time.

MEDICAL CARE FOR DEPENDENTS OF SERVICE MEN

The general attitude of the Association is that where possible, medical care for service men's dependents should be provided by civilian physicians.

The complete proceedings of the House of Delegates are published in issues of the Journal shortly after each meeting and I would recommend that members of the Association read them.

W. A. Wright, M.D., Delegate

Medical Center Adivsory Council

The medical school at the University of North Dakota has made progress during the past year. Under the able leadership of the Dean, Dr. T. H. Harwood, the faculty has been strengthened and the curriculum has been modified. Graduates of the school have little or no difficulty obtaining entrance into four-year medical schools for their clinical training. The clinical clerkship program has been a success, due to the willingness of busy practitioners in the various hospitals to give generously of their time. As a result of this practical experience in the care of hospitalized patients, many of the recent graduates have stated that they have been better prepared for their clinical training than the juniors of some of the four-year institutions.

The mandate of the 1953 legislature, that the medical school be expanded, beginning with a junior class in 1955 and a senior class in 1956, posed a great problem. Those who were realistic—including the entire membership of the advisory council—agreed that it would be virtually impossible to comply with this mandate. In order to be sure that this position was sound, Dean Harwood undertook an exhaustive study of the situation in North Dakota, including the possibilities for decentralized clinical training of the third and fourth year students. He concluded that it would be practically im-

possible to utilize the local hospitals scattered throughout the state for this purpose. Unfortunately, Grand Forks does not have sufficient teaching material to satisfy the need for adequate clinical instruction of third and fourth year medical students. He learned that most physicians in the state are ready and willing to lend support to any program which will ultimately result in the development of an accredited four-year medical school but do not believe it can be done in a short period of time; others are skeptical. He developed an eight-point program necessary in the sound development of the third and fourth years—a copy of which will undoubtedly be included in the report of the special council meeting held in Grand Forks on July 19, 1954—which was approved by the council of the North Dakota State Medical Association. A steering committee was established, having a representative from the University Administration, Board of Higher Education, Medical Center Advisory Council, and the North Dakota State Medical Association. The purpose of this steering committee was to aid in telling the story of the medical school to the people of North Dakota, in order that those who feel that there has been undue delay in the development of a four-year school will understand the impossibility of complying with the mandate of the 1953 legislature. As a result of this realistic approach to the problem there was no attempt on the part of the 1955 legislature to reopen the question and to introduce bills which would force the issue. Much credit is due to Dean Harwood for this result. I believe it is safe to say some of the legislators who had been politically inspired rather than practical in their approach to the problem seem to have seen the light and are willing to allow an orderly program of development to be carried out.

In order to strengthen the clinical departments of the present two-year school, and looking forward to the ultimate development of a four-year school, Dean Harwood has proposed that a rehabilitation center be developed including an out-patient department for such clinics as mental health, alcoholism, crippled children, rheumatism and arthritis, and, if possible, the student health service. He is hopeful that federal funds in the form of Hill-Burton money will be made available to assist in the cost of construction of facilities for a rehabilitation center and the care of the chronically ill, at the University. He points out that there is need for out-patient facilities at the University. There is a state-wide clinic setup for mental health but there is no place at the University where such an out-patient clinic can be held. The cerebral palsy clinic was held at the School of Medicine last fall only because there was space available in unequipped laboratories of the new bulding. This suggestion has great merit because the diagnostic team that is needed to run a rehabilitation center is essentially the same as that needed to teach medical students.

Dean Harwood recognizes the need for an expansion of the clinical faculty at the medical school. However, this cannot be accomplished until there are patients and hospital beds available for teaching purposes. Unfortunately, the state hospitals are widely scattered and their facilities are not readily available to third and fourth year students. It is apparent that some type of hospital facility must be available in Grand Forks for teaching purposes if a four-year school is to be developed. A rehabilitation center and hospital for the care of the chronically ill patients, located at the University, would seem to be the logical answer.

The decreasing number of qualified applicants for admission to our medical school is a serious problem. This is also true throughout the nation. There are undoubtedly many reasons for it, but we must encourage more qualified boys and girls to prepare themselves for medicine as a career if the high standards of medical practice to which our people are accustomed and entitled are to be maintained. There is no shortage of physicians in this country, but there is a shortage of qualified applicants for entrance to medical schools. As physicians, we can do much to encourage bright young boys and girls in our communities to enter medicine. Unless we do, our schools will be forced to admit students who are not properly qualified.

Recommendations:

1. That the North Dakota State Medical Association continue its support of a realistic approach to the problem of expansion of the present two-year medical school to a four-year accredited institution.

2. That physicians throughout the state of North Dakota be urged to encourage eligible boys and girls to apply for admission to the medical school.

L. W. Larson, M.D., Representative

Committee on Medical Education

Dean T. H. Harwood, on December 11, 1954, gave the following report as to the present status of the medical school.

REPORT FROM THE DEAN OF MEDICINE

1. Our present status. We have, as you know, a two-year school approved by both the Association of American Medical Colleges and the Council of Medical Education and Hospitals of the A.M.A. Our school is doing an excellent job of teaching — all our students in recent years have been successfully transferred and no student has failed after transfer in the past eight years.

We have 40 freshmen and 40 sophomores enrolled at present, and 21 North Dakota resident applicants accepted for the class coming in in September. The school of medicine is also teaching courses in anatomy, chemistry, bacteriology and physiology to medical technologists, occupational therapists, home economics and physical education majors, the University nurses, and student nurses from our local hospitals. This provides $50,000 worth of training which would otherwise be added to the University budget.

2. The secretary of the Association of American Medical Colleges, who is very familiar with our situation and who has visited our campus before inspection, when asked whether or not he felt it was possible to have a four-year school, said he felt it was possible. He felt it could not be hurried and recommended that we build up a residency program as the first step, not only to develop a group of young men who could serve later as teachers, but which would bring doctors into North Dakota at the end of their training, and they would be more likely to settle here. The third dividends from this program would be better medical care to the people of the state.

3. Clinical facilities. At the present time, facilities necessary for teaching the third and fourth years are not available, and there is considerable work and planning before they can be developed. I use the word developed because construction of such facilities without regard to cost or to the way in which they will fit into the state program for medical care would be outrageously expensive and wasteful. We must not create white elephants. Our local hospitals are efficient, well run and well staffed. They are designed to take care of local needs, and the turnover of patients is rapid. There are no resi-

dents in our local hospitals and only one intern, that at the Deaconess.

The state medical facilites are scattered. If the tuberculosis hospital, the mental hospital, and the veterans hospital were in the University area, we would have a solid nucleus of patients around which to build a teaching program. Since this is not so, we must look elsewhere.

4. Other expansion programs. The states of Mississippi, Missouri and West Virginia are at present converting two-year medical schools into four-year schools. They have been between five and ten years in their planning. The University of Mississippi is completing the construction program of its new hospital and medical school building at Jackson. Jackson is a town of 110,000, located in the center of the state, and its hospital will fill a need which the state has for more hospital beds. This construction program is costing about $9,000,000.

Missouri: The legislature has appropriated $13,500,000 for the building program now underway at Columbia, Missouri. Of this, $9,000,000 is for hospital construction and $3,100,000 for a medical science building and servicing plants. The hospital has 441 beds.

West Virginia, which has been collecting $4,000,000 a year from a soft drink tax, for five years, has, at present, the heating plant installed, and is digging the foundation for their hospital. The building will be completed in 1957. No definite date has yet been advanced for registration of the first third-year class.. All of the above programs involve the constructing of a university hospital. Here in North Dakota, the construction of 23 small hospitals scattered throughout the state within the past ten years, makes such a proposal impracticable. It would mean duplication of facilities, which no state can afford.

5. Faculty needed for expansion. No clinical faculty has been hired as yet, since they cannot work or organize their work in the absence of patients and patient beds. Many of the doctors of North Dakota are fully competent and able to teach. The problem is that they are all busy practitioners, and no busy practitioner can possibly devote the four or five afternoons a week, at a minimum, to teaching without either help in doing his work or replacement. It will be necessary to employ a clinical staff of part time and full time men.

6. Funds. At the present time, the cost of our medical school compares favorably with the cost of other two-year schools and with the cost of the first two years at Vermont, with which I am familiar. It is practically impossible to compare costs of medical schools because of the variety of bookkeeping methods. For example, some medical school budgets include no building overhead, and the library may or may not be included. Our over-all budget, including the blood bank, the school of nursing, and the service courses, leaves a surplus from the mill levy. This surplus is just about enough to hire clinical men to do the teaching for the third and fourth years. However, it allows nothing for hospitalization costs, which, for a school of this size, would run to about $1,200,000 per year.

7. I have been trying to work out a program which would bring patients to one area to provide teaching material. The diversity of our medical facilities makes this difficult. The field of rehabilitation is one area in which we can accomplish our needs; not only to create clinical facilities, but to fulfill a need which the state has and which will continue in the future. Medical students teaching in the field of rehabilitation is increasing the country over. There is a $2,500,000 rehabilitation center just opened in Minneapolis, which is part of the teaching facility at the medical school there. Medical students must be taught in the field of rehabilitation because, as our population gets older and we have fewer people dying of acute diseases and injury, our rehabilitation problems will be greater.

The diagnostic team needed to run a rehabilitation center is the same team as that needed to teach. All fields of medicine have to be represented. Furthermore, the University, if it is to take its place among the universities of the country as a university and not a college, needs the clinical material to complete their programs in psychology, sociology, physical therapy, occupational therapy, nursing, and medical technology. The rehabilitation division of the state of North Dakota is here at the University and is in need of facilities.

We need outpatient facilities at the University. We have a state-wide clinic set-up for mental health, but there is no place at the University where such an outpatient clinic could be held. We were able to hold a cerebral palsy clinic at the school of medicine last fall only because our laboratories in the building are still empty.

I propose that we plan the development of a rehabilitation center, including an outpatient department for such clinics as mental health, alcoholism, and crippled children, rheumatism and arthritis, and if possible, the student health service. Federal funds in the form of Hill-Burton money next year are available for the construction of facilities for the chronically ill, rehabilitation centers, and examination and treatment centers. There are $300,000 of these funds available to North Dakota as matching funds, and I believe this would be a wise use of them. We must, if we are to carry out the wishes of the people, stop dissipating for clinical medical facilities.

8. We must have a good medical school and good medical education. Not only are the people of North Dakota worthy of good medical care, but if we do not have a good school we will have no students. They will go elsewhere.

When people ask me what is the attitude of the doctors of the state, I tell them that many of them are skeptical about the possibility of a four-year school because of our population and geography. However, the physicians of this state are in favor of good medical education, and my proof that they are willing to sacrifice to that end, its the high quality of teaching, the time given freely and without pay by them to the students during their preceptorships in the various areas of the state. I am hopeful in the future that our fourth year students may be taught, to a large degree, in other areas of the state.

I do not, at the present time, see how we can possibly make the deadline in September 1955 for a third year. I have had the students apply for transfer for this reason. I sincerely hope that the people of North Dakota allow us to develop our facilities and build soundly, rather than to insist on too rapid expansion.

I have never asked a doctor in North Dakota to do anything for the medical school, but what that service was rendered wholeheartedly and promptly, and I want to thank all of you for that cooperation.

T. H. Harwood, M.D., Dean

On December 11, 1954, a combined meeting of the Committee on Medical Education and Public Policy and Legislation was held in Fargo. The minutes of this meeting at the Gardner Hotel, Fargo, North Dakota, December 11, 1954, are as follows:

Committee on medical education. Members present: T. H. Harwood, M.D., J. H. Mahoney, M.D., T. E.

Pederson, M.D., F. D. Naegeli, M.D., W. E. G. Lancaster, M.D., Ralph Leigh, M.D., L. H. Kermott, Jr., M.D., Robert Painter, M.D.

COMMITTEE ON PUBLIC POLICY AND LEGISLATION. Members present: O. W. Johnson, M.D., Amos Gilsdorf, M.D., D. J. Halliday, M.D., V. J. Fischer, M.D., W. E. G. Lancaster, M.D., J. N. Elsworth, M.D., W. H. Gilsdorf, M.D., C. A. Arneson, M.D., Louis Pine, M.D., Keith Vandergon, M.D., R. O. Gochl, M.D.

Others present were: Drs. P. H. Woutat, J. C. Fawcett, O. A. Sedlak, Nelson Youngs, and Mr. Lyle A. Limond, executive secretary.

The combined meeting was called to order at 2:20 P.M. by the chairman of the Committee on Public Policy and Legislation, Dr. O. W. Johnson of Rugby.

Dean T. H. Harwood was called on to give an up-to-date picture of the medical school. Dr. Harwood stated that:

1. Additional equipment was still arriving for the expanded facility.

2. Twenty-one students have now been accepted for the 1955 freshman class.

3. The status of the third and fourth years is as follows: (a) out of the question for 1955 and 1956, but not for a future date; (b) development of a residency program is essential; (c) there is a possible entre through the field of rehabilitation; (d) mill levy funds are available above current needs and are being husbanded; (e) the thirty-fourth session of the Legislature must be told that there will not be a four-year school by 1956; and (f) physicians' attitude is a positive one—if we have a four-year school, it must be a good one with a competent staff, good facilities, and with clinical material present, since you cannot teach medical students without hospital teaching beds.

The combined meeting was adjourned to 3:10 P.M., with the members of the Committee on Medical Education moving to Parlor A for a meeting of their own.

The Committee on Public Policy and Legislation remained in the East Room for its meeting.

Following the meeting of the two committees, a separate meeting of the Committee on Medical Education was held on December 11th at the Gardner Hotel. The minutes of this meeting are as follows:

Committee on Medical Education Meeting

The meeting at the Gardner Hotel, Parlor A, in Fargo, North Dakota, December 11, 1954, was called to order by Dr. T. H. Harwood, acting chairman in the absence of Dr. H. M. Berg. Dr. Ralph Leigh acted as secretary.

The following committee members were present: Drs. T. H. Harwood, Ralph Leigh, Robert Painter, L. H. Kermott, Jr., F. D. Naegeli, W. E. G. Lancaster, T. E. Pederson, and J. H. Mahoney.

Dr. Harwood distributed reprints of the Alumni Bulletin dealing with the growth of the University of North Dakota Medical School, as well as the Public Affairs Pamphlet No. 214, entitled "The Challenge to Medical Education," by Robert M. Cunningham, Jr., a lay author.

Discussion centered on the question of the ways and means of putting the problem of the growth of the medical school from a two-year to a four-year school before the physicians and legislators of the state. Each member of the committee present stated that, if at all possible, he would contact his district legislators to find out just exactly what the legislators would like to know concerning the school of medicine.

A question and answer bulletin as an education device was next discussed. The following points were deemed essential in such a bulletin:

1. Physician distribution in 1920, 1940 and 1950.
2. Educational requirements for M.D. degree, in 1920, as compared to present day.
3. How a community goes about obtaining a physician.
4. Needs of a community to properly support a physician.
5. Private enterprise motives to be stressed.
6. Positive approach by medicine toward a four-year school when practical.
7. Stress requirements in having an accredited four-year school, e. g., monies, faculty, hospitals, clinical material, etc.
8. Intent of persent one mill levy being satisfied.
9. Compared North Dakota situation to other states, e. g., law tuition rates in North Dakota. Consolidation with South Dakota was discussed.
10. Why Grand Forks hospitals cannot fulfill the medical school needs. Dr. Harwood mentioned rehabilitation needs in North Dakota and how this program could be worked into the present two-year school set-up.

Drs. Harwood and Leigh are to prepare the question and answer bulletin.

Discussion also brought out the observation that North Dakota has private clinics caring for the diagnostic needs, which is not true in Vermont and many other eastern states.

This committee recommends that the Committee on Public Policy and Legislation make efforts to revise the present law as embodied in Senate Bill No. 184 of the 33rd Legislative Assembly to read "there shall be a four-year school of medicine as soon as practical." Keep other provisions.

Meeting adjourned at 5:25 P.M.

The information that Dean T. H. Harwood sent to the members of the State Medical Association and all members of the Thirty-fourth Legislative Assembly must have had a profound effect on public opinion.

No mention whatsoever was made of the third or fourth year medical school at the recent session of the Legislature.

It is the opinion of the North Dakota State Medical Association Committee on Medical Education that Dean Harwood has performed his tasks in an exemplary manner.

H. M. BERG, M.D., Chairman

It was moved by Dr. Peters, and seconded by Dr. Vandergon, that the reports of the standing committees, except the committees on Medical Education, Medical Economics and its sub-committees, be referred to the Reference Committee Number Four. Motion carried.

Speaker Dodds next inquired of the House of Delegates their wishes regarding the reports of the Delegate to the American Medical Association, the Medical Center Advisory Council, and the Committee on Medical Education. Dr. Jacobson moved that these reports be referred to the proper Reference Committee, Number Three, and the motion was seconded by Dr. Hawn. Motion carried.

Committee on Cancer

Your committee on cancer had 4 meetings last year through the medium of the North Dakota Cancer Society. As the activity of cancer detection has increased in the United States, likewise has the tempo of activity increased in North Dakota. A vigorous program is being carried out from the smallest township to the largest city. This is achieved by means of lectures, the showing

of sound films, the distribution of literature, group meetings at 4-H Clubs, etc., and presenting cancer symposiums to the busy North Dakota doctor. Cancer continues to be a major cause of death in North Dakota. During the year 1954, it is estimated that there were approximately 2,000 cancer cases and 600 cancer deaths. This, together with the high morbidity, continues to constitute one of the real problems confronting the North Dakota doctor and public.

The rapid increase in deaths from cancer of the lung is a matter of concern to those who guide the policies of the American Cancer Society, the North Dakota Cancer Society and your committee on cancer. Thanks to Jerome Svore, director of public health; Ken Mosser, director of preventable diseases; and Ray Kohoutek, technician, the Mobile X-ray Unit visited nine cities in North Dakota during the tour of the Cancer Caravan. Through their splendid cooperation and untiring efforts, over 7,000 chest x-rays were taken. These films were interpreted by qualified radiologists for any abnormality—cancer, tuberculosis or a heart ailment. At the time of writing, this policy will again be carried out, in March 1955, and statistics for the two years will be published in the next report from the committee on cancer.

Top speakers were obtained for the Cancer Caravan during 1955. This tour began in Williston on March 22, with speaking engagements in Minot, Devils Lake, Grand Forks, Fargo, Valley City, Jamestown, and Bismarck, and terminating in Dickinson, April 1st. The northern route was fortunate in obtaining Dr. E. H. Soule, surgical pathologist at the Mayo Clinic, who spoke on Cytologic Examination of Smears from the Cervix and Sputum and also discussed Examination of Fluids from the Stomach, Urinary Tract and Abdomen. His partner, Dr. Donald Childs, Jr., also of the Mayo Clinic, discussed the Role of X-ray in the Over-All Program for Treatment of Carcinoma of the Breast and the use of Various Hormones in the Palliative Control of Such Diseases. The Fargo to Dickinson tour was honored by the presence of Dr. Arnold J. Kremen and Dr. Morton M. Kligerman, who, at the present time, are members of the Columbia University Medical School and also attending doctors at the Presbyterian-Columbia Medical Center and the Frances Delafield Hospital of New York. Dr. Kremen discussed the Surgical Management of Carcinoma of the Breast, and Dr. Kligerman discussed Radiological Treatment of Carcinoma of the Breast and the use of the Various Hormones in the Palliative Control of Such Diseases. These stimulating lectures were well attended, which has encouraged the Cancer Society to continue this type of education as long as this response continues.

During the past year the North Dakota Cancer Society continued the policy of sponsoring a cancer lecture for the North Dakota State Medical Meeting and also for the North Dakota Society of Obstetrics and Gynecology. At the time of writing, the speaker for the North Dakota State Medical Meeting has not been announced. Last September, 1954, at the obstetrical and gynecological meeting in Williston, Dr. Franklin L. Payne, chairman of the Department of Obstetrics and Gynecology at the University of Pennsylvania School of Medicine, presented the third Leonard W. Larson cancer lecture, "Adenocarcinoma of the Endometrium." We hope the board of directors will see fit to also continue this type of cancer education in bringing eminent cancer speakers to our state meetings.

During the past six years, approximately $100,000 has been given to research study at the University of North Dakota and the North Dakota Agricultural College. At the January meeting in 1955, a grant in aid of an additional $4,000 was presented to Dr. Miller of the North Dakota State College to continue his studies in urethane.

Nationally, the American Cancer Society has appropriated a fund of $500,000 earmarked for the support of fundamental investigations of the causes of lung cancer. During 1954, the relationship between human smoking habits and death rates were carried out by 22,000 volunteer researchers of the American Cancer Society in ten divisions: California, Illinois, Iowa, Michigan, Minnesota, New Jersey, New York, Pennsylvania, southeastern Michigan, and Wisconsin. Their findings were based on the study of 187,766 white men between the ages of 50 and 69. Death increased with the amount of cigarette smoking. Disease of the coronary arteries was indicated as a primary cause of death of 2,147 men. Cancer was indicated as a primary cause of death of 844 men. This survey will continue and at least another year of follow-up will be required before any relationship can be properly evaluated.

Recently the writer received a book under the title, "Krebiozen, Key to Cancer?" by Herbert Bailey, published by Hermitage Press. This has been reviewed by newspapers throughout the country. This book was not at all impressive. Dr. Charles Cameron, medical and scientific director of the American Cancer Society, aptly summarized the contents of the book in stating, "Krebiozen was introduced to the public on the premise that it would never be fairly received or tested. Ignoring the customary methods of quietly conducting clinical trials, originators of this proposed cancer treatment persuaded a distinguished scientist to go along with them in the widely publicized and ballyhooed debut in the form of a hotel ballroom sales promotion stunt and an expensive appearing brochure, with others to follow. This was not the manner in which reliable and authentic compounds are given to the public to fight disease. Such wonderful drugs as the sulpha compounds, antibiotics, the hormones, were quietly tried on thousands of cases before the public was informed of their usefulness as therapeutic agents. Even so, had Krebiozen been a worthwhile treatment for cancer, by now its efficacy would be well known. It has been available to doctors for several years. It has had a series of tests reported by the American Medical Association and by a committee of the National Research Council and declared to be without merit as a therapeutic treatment for cancer."

Possibly the treatment of cancer with "Laetriles" during the past year has come to the attention of the medical profession in North Dakota. A circular letter was received and a report by the cancer commission of the California State Medical Association which demonstrates the exemplary manner in which one state medical society has assumed responsibility for arriving at opinions, at least tentatively, concerning the value of certain newly devised cancer "treatments," originating within its purview. A new Laetrile was synthetized by Mr. Ernest T. Krebs, Jr., designated roughly as Beta-Cyanophoric-Glucuroniside which in the presence of an enzyme, Beta-Glucuronidase released quantities of nascent hydrogen cyanide which would be lethal to the cancer cell. Methodically and systematically, the cancer commission investigated the nature of the treatment method, proponents of Laetrile treatment, experimental evidence offered, clinical evidence offered by proponents of Laetrile, autopsy data, clinical evidence discovered by the cancer commission, a complete investigation-observation of 44 cases treated with Laetrile, and autopsies reviewed by the cancer commission. The commission concluded that no satisfactory evidence has been produced to indicate any significant cytologic effect of Laetrile on the cancer

cell. Their method of investigation should serve as a guide to any state cancer commission to properly investigate any so-called cancer treatments that originate in our midst.

The North Dakota Cancer Society announces that their quota for the year 1955 is in the neighborhood of $95,000. As in the past, the North Dakota State Medical Association has given its complete endorsement to the program and it is hoped that this endorsement will continue. The North Dakota physician is urged to cooperate with the county workers in helping the society to gain this goal. Our efforts may seem insignificant. We are not cancer specialists, but we hear and read of the enormous expenditure of time, research, intelligence and money. Today less than 1 per cent of all cancers have a known, or even suspected cause. Yet this etiologic fraction of 1 per cent is the first wedge of knowledge into a heretofore impenetrable mystery. That the specialists in cancer have been able to identify even this small part of the causes of cancer is a great step forward in the greatest of all battles of man against his environment—the battle against cancer.

C. M. Lund, M.D., Chairman

Committee on Crippled Children

The meeting of the committee on crippled children was held at the Gardner Hotel, Fargo, North Dakota, December 11, 1954. Members of the committee present were: Drs. L. G. Pray, Fargo, chairman; C. G. Johnson, Rugby; B. A. Mazur, Fargo; H. J. Fortin, Fargo; Louis Silverman, Grand Forks; A. E. Culmer, Jr., Grand Forks; and Paul Johnson, Bismarck.

Others present were: Drs. P. H. Woutat, president, North Dakota State Medical Association; and D. J. Halliday, president-elect. Mr. Lyle A. Limond, executive secretary, North Dakota State Medical Association, was also present, and acted as secretary for the meeting. One hundred per cent of the committee members were present.

The committee felt that their recommendation of January 30, 1954, to the North Dakota State Medical Association regarding help being obtained from benevolent organizations, such as the Elks Clubs, for the purpose of securing possible financial aid for children suffering from rheumatic heart disease, epilepsy, and possibly other crippling conditions, should be re-emphasized.

Dr. Paul Johnson explained how the special advisory committee to the crippled children services division of the North Dakota Department of Public Welfare came into being. He stated that it was an outgrowth of activity by the U. S. Children's Bureau. The regional office of the U. S. Children's Bureau for this area is at Kansas City, Mo., and the director is Maisel Williams, M.D. The plan is to attempt the formulation of a better program for the crippled children services in North Dakota. Plans are being laid to send children suffering from congenital heart conditions to a free clinic in Chicago. North Dakota is still using the facilities available at the Mayo Clinic and the University of Minnesota. Dr. Paul Johnson stated that transportation costs have not been paid by the crippled children services division of the State Welfare Department.

It was recommended by the committee that Dr. Paul Johnson see what Minnesota can do to match the Chicago plan.

The committee felt that the resolution passed on January 30, 1954, regarding an educational effort to alert district medical societies as to the work of the crippled children services be re-emphasized.

The committee next discussed the status of cerebral palsy in North Dakota. Dr. Pray felt that the public should be informed that cerebral palsy is treated as one of the diseases of childhood in the same way as poliomyelitis or rheumatic heart disease, and not as a separate specialty in itself necessarily. He mentioned the presence of an organizer from the United Cerebral Palsy Association in the state, who has been seeking funds for his Association, and attempting to organize fund drives in the various communities in the state. In view of this situation, which seems unjustified to the committee, it was recommended that more education be given the public regarding various crippling conditions. It was suggested by committee members that television broadcasts and public forums would be effective means of reaching the public. Contact was to be made with Mr. William Unti of the North Dakota Society for Crippled Children and Adults, and Mr. James Fenelon of the Polio Foundation in this regard.

It was the opinion of the committee that the annual cerebral palsy clinic which has been held each fall for the past several years should be continued, and that the University of North Dakota is the ideal place to continue to hold these clinics. Dr. Harry Barnett, orthopedist and cerebral palsy specialist from Chicago, conducted the clinic on November 15 and 16, 1954; 20 children were examined by Dr. Barnett with an excellent discussion of each case for the visiting physicians, medical students and other professional personnel. In view of the valuable type of presentation given in these cases, the physicians of North Dakota are urged to attend these clinics. Notices will be sent to all members of the State Medical Association as soon as the time and place have been set for the clinic this fall. Dr. Silverman suggested that several of the cases presented by Dr. Barnett last fall be published in the Journal-Lancet. Dr. Barnett is to be contacted to see whether he would be willing to do this.

Epilepsy as a crippling disease was discussed with regard to making a proper diagnosis and giving adequate treatment to all cases. The committee recommended that a paper on epilepsy be presented every few years at a meeting of the North Dakota State Medical Association as a means of informing the profession more adequately concerning this disease. This suggestion was made by Dr. Halliday.

L. G. Pray, M.D., Chairman

Committee on Industrial Health and Trauma

I am submitting a brief report on the activities of the committee for which I was named chairman for the year 1954. First, I would like to say that the committee did not have a formal meeting during the year for the simple reason that none was called by the chairman. It was intended that the committee try to promote a farm safety program last summer but it seemed that personal affairs took up so much time that the writer did not get around to organizing a meeting. It is still my idea that this is a worthwhile project and the chairman of this committee would appreciate any suggestions from the other members of the committee as to how we might go about this for the coming year.

It was also the intent of the writer to make use of the records at the State Workmen's Compensation Bureau for the purpose of making a survey of the relative quality of medical care being received by the patients in North Dakota by local physicians under Workmen's Compensation liability. This was taken up with the Workmen's Compensation Bureau chairman, Mr. Otis Bryant, who gave the writer, who is also medical director of that organization, very little encouragement. It was

the intent of the chairman to start this survey about the first of the year without assistance from the statistical department of the compensation bureau. As you probably read in the papers, there was a legislative committee appointed to investigate the workings of this organization during the recent session of the legislature. Because the chairman did not wish to become involved in any political controversy, it was felt that this was not the proper time to make this survey because of possible political implications or accusations which could possibly be made about this study even though it was to be done on a purely scientific basis.

The chairman wishes to express regret that this committee has been relatively inactive through no fault of the individual members.

RALPH VINJE, M.D., Chairman

Committee on Maternal and Child Welfare

The committee on maternal and child welfare of the North Dakota State Medical Association met in Bismarck in August 1954 with Dr. Madelene Donnelly of Des Moines, Iowa, and Dr. Maysil Williams of Kansas City, Mo., both of whom have had considerable experience in maternal mortality surveys. After the meeting, the committee drew up the following proposed plan which has been accepted and approved by the North Dakota Society of Obstetrics and Gynecology. We urge its adoption by the North Dakota State Medical Association.

PROPOSED MATERNAL MORTALITY SURVEY

1. Definition: To include any woman who dies during pregnancy, including an ectopic pregnancy, abortions, and up to six months postpartum. This includes any death due to complications of pregnancy, and accidents or suicides or any woman who dies of natural causes during the same period of time.

2. The purpose is to improve the quality and standards of obstetrical care throughout the state and to reduce maternal mortality.

3. Responsibility: This is a joint effort between the Committee on Maternal and Child Welfare, North Dakota Society of Obstetrics and Gynecology, and the North Dakota State Medical Association.

4. Duty: There will be obstetrical men strategically located, such as in Minot, Bismarck, Fargo, Grand Forks, Williston, and Dickinson. This should divide the state, so that the responsibility and work will be equally divided. (a) Consultants: Consultants will not investigate any death in their own city. This should be done by the closest consultant in that area. (b) Review board: This is composed of one representative of each medical society district, and is to review cases submitted to it without identity revealed, and is to decide upon the degree of patient and physician responsibility. (c) Coordinator: A man, to be selected, who will prepare each case after going over the records furnished by the consultant and delete all information regarding patients—namely, location and doctor involved. He will then present the case to the review board. This man probably should have some connection with the state health department, even if only a token title from the State Board of Health.

5. Finance: (a) Mimeograph work to be done by the health department. (b) Secretarial work to be done by the health department. (c) Honorarium and travel expense to be arranged with and through the state health department.

6. Reporting: Hospitals must report their maternal deaths within forty-eight hours. Doctors' report of deaths should be in within forty-eight hours, and also a report from the State Health Department. Coroners to report within forty-eight hours all non-hospital maternal deaths.

7. Education: This survey should bring before the medical profession and the public the needs for adequate care during pregnancy and the postpartum period, as well as the preventability of maternal deaths.

On the 9th of March, we again met in Bismarck with the public health committee of the State Medical Association and members of the State Health Department to consider the proposed use of Dr. Salk's polio vaccine. This vaccine will be used on all first and second grade school children in North Dakota, with the permission of the parents. The two committees, after discussing the results of last year's immunization program in the three test counties, have unanimously approved its use this year if it is licensed.

ROBERT E. LUCY, M.D., Chairman

Committee on Necrology and Medical History

(1955)

I want to give to others hope and faith;
I want to do all that the Master saith;
I want to live aright from day to day;
I'm sure I shall not pass again this way.
(Anonymous)

CARL E. ELOFSON, M.D.

Dr. Carl E. Elofson, 55, Fargo physician since 1929, died unexpectedly Saturday, May 8, 1954.

He was born October 14, 1898, at Wheaton, Minnesota, and attended public school at Fergus Falls, Minnesota. He received his bachelor of arts and bachelor of science degrees from the University of North Dakota and his medical degree from the University of Kansas. He interned at St. John's Hospital in Fargo and was on the St. John's medical staff.

He served three terms as Cass County coroner, from 1933 to 1939. Dr. Elofson was a member and former vice-president of the Cass County Medical Society, a member of the North Dakota State Medical Association, and a fellow in the American Medical Association.

He was a member of several Masonic bodies and the El Zagal Oriental Band. He had been a deacon of the First Baptist Church. Dr. Elofson was commissioned in the Naval Reserve Medical corps in 1942 and, at the time of his death, was still in the reserve with the rank of commander.

Surviving are Mrs. Elofson; two sons, Carl, a student at NDU, and Stanley, a student at NDAC; and a daughter, Dorothy.

WILLIAM E. LONGSTRETH, M.D.

Dr. William E. Longstreth, retired Kensal physician, died April 22, 1954 of a heart attack in Los Angeles, California, where he had been visiting.

Dr. Longstreth had retired from the practice of medicine several years ago.

A native of Moxahala, Ohio, he was graduated from Starling Medical College, Columbus, Ohio, in 1896. He practiced in Ohio six years and in 1902 came to Kensal. In 1946, he was honored by residents of that community for fifty years of medical service.

Dr. Longstreth was president of the Kensal School Board thirty years, and a member of the Kensal Methodist Church. Surviving are two sons, Gordon, in Michigan, and George Eldon, former Fargo attorney, now of Riverdale, N. D., and a daughter, Ione, of Seattle, Washington.

JOSEPH J. STRATTE, M.D.

Dr. Joseph J. Stratte, 67, practicing physician and surgeon in Grand Forks since 1932, died unexpectedly in Minneapolis, April 10, 1954.

Born February 19, 1887, at Dawson, Minnesota, Dr. Stratte received his early education there and attended

high school at Willmar, Minnesota. He graduated from the University of Minnesota with a B.A. degree in 1911, and with his M.D. in 1915, and interned at University hospital in Minneapolis until 1918.

Dr. Stratte was licensed to practice in Minnesota in 1915 and was assistant to the chief of surgery at the University of Minnesota hospital from 1918 through 1922. He practiced for about ten years at Hallock, Minnesota, before coming to Grand Forks. He was licensed to practice in North Dakota in 1932.

He was a member of the staff of St. Michael's and Deaconess hospitals in Grand Forks. He was also on the staff of the Kittson War Memorial Hospital at Hallock, Minnesota. He was a specialist in urology.

His first wife, the former Blanch Barnett, died in 1932. Dr. Stratte married the former Irene Dille, September 30, 1940, at Grand Forks.

He was a member of the United Lutheran Church, the Grand Forks District Medical Association, the North Dakota-Manitoba Urological Society, North Dakota State Medical Association, and was a fellow in the American College of Surgeons.

Survivors include his wife; four children by his first marriage, Dr. John Stratte of Enumclaw, Washington, Dr. Paul Stratte of Redding, California, Mrs. B. M. Griffin (Elizabeth) of Mauston, Wisconsin, and Mrs. E. L. Billing (Patricia) of San Francisco, California.

J. F. TIMM, M.D.

Dr. J. F. Timm passed away March 23, 1954 in a Minot nursing home. He was 86 years old.

Born in Hanover, Germany, June 28, 1867, he came to the United States in 1884. He received his medical education in Chicago. With his wife, who preceded him in death, he homesteaded at Emmett, North Dakota, in 1906. He moved to Makoti, North Dakota in 1919 and lived there until 1945. After making his home at Portland, Oregon, he returned to Emmett in 1951. He was a physician at Emmett and Makoti for half a century.

He was honored by the North Dakota State Medical Association when he became a member of the "50-Year Club" in 1945, and was also an honorary member.

Surviving are a son, Dr. Herman Timm of Portland, Oregon, and a daughter, Mrs. Melvin Bjornholt, Emmett, North Dakota. He had four grandchildren.

G. J. McINTOSH, M.D.

Dr. G. J. McIntosh, 77, retired Devils Lake physician and surgeon who practiced in Ramsey County for over forty-five years, died December 15, 1954, at a convalescent home in Devils Lake.

Born August 12, 1887 in Glengarry, Ontario, he attended elementary schools there and graduated from the McGill University school of medicine in 1905. He started his practice in Webster the same year and moved to Devils Lake in 1907.

Dr. McIntosh was a charter and honorary life member of the Devils Lake Elks Lodge, serving as its third exalted ruler. He was county health officer for forty years.

He was preceded in death by his wife, the former Mabel J. Colson, whom he married December 25, 1909, at Minneapolis.

Surviving are one daughter, Mrs. William Connally of Devils Lake, with whom he had made his home, and one son, Donald, of Spokane, Washington.

C. C. CAMPBELL, M.D.

Dr. C. C. Campbell, 77, who had been living with his son, Colin C. Campbell, Jr. of Rome, New York, and had been in failing health for several months, died July 9, 1954.

He recently retired from practice at Ashley, North Dakota, and was honored by the residents of Ashley in a community service on Dr. Campbell Day, May 10, 1954. Several speakers touched on the highlights of the doctor's life, which took him from Iowa to Ashley in 1909 to set up practice, lasting 44 years.

As a typical country doctor in his early years, he travelled throughout the county in horse and buggy in the summer and sleigh in winter to treat patients and deliver babies. He was often referred to as the community's guardian of health.

Dr. Campbell was born in Listowel, Ontario, Canada, March 30, 1876. He was graduated from the Toronto School of Medicine in 1901, setting up his first practice at Hermansville, Michigan. He later spent a short time in LeMars, Iowa, migrating to Ashley in 1909.

Surviving in addition to his son, are his wife, the former Anna Belle Cunard, whom he married in 1904 in Hermansville, Michigan, and who resides with their son in Rome, and a daughter, Mrs. Ross LaLonde, Hollywood, California.

H. J. GOWENLOCK, M.D.

Dr. H. J. Gowenlock, 73, assistant superintendent of the North Dakota State Hospital in Jamestown, and formerly of Gardner, North Dakota, died July 3, 1954, in Jamestown. He had been in poor health for the past four years.

Dr. Gowenlock came to the state hospital in 1946 from Gardner, N.D., where he had been a physician for forty-two years. When he left Gardner, the residents gathered at the community hall, which he helped build, and paid tribute to him in a farewell party attended by many hundreds. He was an ardent sports and bridge fan, holding the state bridge championship for two years. He became active in rural electrification through noting the absence of electric power on farms he visited in making his calls. He personally signed up many farms for REA.

Dr. Gowenlock was born in Chicago, Illinois, November 26, 1880. He came to Barnesville when a child. He was a graduate of the Barnesville High School and University of Minnesota School of Medicine in 1904. He completed fifty years of medical practice in North Dakota in July 1954. He was a member of the First Congregational Church of Jamestown. He was also a member of several Masonic bodies.

Dr. Gowenlock and Miss Claire Pritchard were married September 24, 1918. Surviving are his widow; two daughters, Mrs. Lloyd Hanson (Jean) San Antonio, Texas, and Mrs. Berger Hagen (Wilda) Seattle, Washington; and four grandchildren.

W. A. LIEBELER, M.D.

Dr. W. A. Liebeler, prominent Grand Forks physician and surgeon, collapsed and died unexpectedly September 22, 1954, while at his office. He was 56.

Dr. Liebeler had recently been undergoing treatment at a Grand Forks hospital for a heart condition. Since his discharge from the hospital, however, he had been carrying on his medical practice. His attending physician gave the cause of death as coronary occlusion.

Active in civic and fraternal circles, Dr. Liebeler was a member of several Masonic orders. He was president of the Shrine Jesters in 1947 and 1948. In 1948 and 1949 he held the presidency of the North Dakota State Medical Association. He was a former member of the council of the association and active in the affairs of the Grand Forks District Medical Society. He also was a fellow of the American College of Surgeons, and the International College of Surgeons. He was a past presi-

dent of the North Dakota Society of Obstetrics and Gynecology, and was very active in its affairs.

Born at Langdon, North Dakota, December 7, 1897, he received his grade and high school education there. In 1917 he entered the University of North Dakota. During World War I he served eleven months as a first lieutenant of infantry in the Army.

In 1922, Dr. Liebeler entered the University of Illinois and in 1925 received his doctor of medicine degree from that school. He also held degrees of bachelor of arts and master of arts from Illinois.

He came to Grand Forks in 1925 and had been practicing medicine since that time.

Dr. Liebeler married the former Frances Pierce of Grand Forks on September 7, 1927 at Minneapolis.

Mrs. Liebeler survives, with two daughters, Katherine and Patricia.

OLAF SAND, M.D.

Dr. Olaf Sand, Fargo physician for a half century, died at the age of 83, at his home, on September 28, 1954.

He was born March 14, 1871, at Sand, Nord Odal, Norway. He attended public school for a short time and later had private tutoring. He registered at the University of Christiania in 1889, and, in 1891, he began the study of medicine. He received his diploma of M.D. in 1897. In July he was married to Eva Crawford, a medical student. He began practice at Hareidland, a rugged island off the coast of Norway, with his wife assisting him by giving the anesthetics at emergency operations. In 1899 they returned to Oslo, he as intern at the government hospital for a year and a half, and she to continue her medical study and receive her diploma of M.D. in 1901. She never practiced.

He began his practice in the United States at Pelican Rapids in 1902. In 1905 he moved to Fargo as a partner of Dr. Tronnes, who had been practicing in Fargo since 1903. Dr. Sand was one of the founders of the Fargo Clinic and of St. Luke's Hospital in Fargo. In 1944 Dr. Sand retired from the Fargo Clinic and from medical practice.

His first wife died in Fargo in June 1941. Their only child, Mrs. Sigmund Leifson (Hedvig) survives.

In 1947, Dr. Sand was married to Prudence K. Gearey, who also survives.

Dr. Sand was a member of the "50-Year Club" of the North Dakota State Medical Association, being so honored in 1949, and was made an honorary member of the association in 1954, a few short months before his death.

WILLIAM A. GERRISH, M.D.

Dr. William A. Gerrish, for many years a physician and surgeon in Jamestown, North Dakota, died at his home in Alhambra, California, February 13, 1955.

Dr. and Mrs. Gerrish went to Alhambra following Dr. Gerrish's retirement. He had been ill for a month.

Dr. Gerrish was born in Minneapolis in 1873. He was graduated from the Minneapolis High School and in 1896 he was graduated from the school of medicine at the University of Minnesota. Dr. Gerrish served his internship at the St. Barnabas Hospital, Minneapolis. He later practiced medicine at Enderlin and came to Jamestown in 1908.

Dr. Gerrish and Dr. P. G. Arzt formed a partnership and took over the practice of Dr. Rankin and Dr. Sifton. Dr. Arzt and Dr. Gerrish organized the Parkview Hospital which was opened in 1913. The hospital was taken over by the Sisters of St. Joseph in 1918 and is now known as Trinity Hospital.

The Jamestown Clinic, of which Dr. Gerrish was a member, was formed in 1920. During the years Dr. Gerrish practiced here he served as Jamestown city health officer and Stutsman County coroner. He served as a member of the board of examiners at the University of North Dakota. He was a charter member of the American College of Surgeons and a past president of the North Dakota State Medical Association (1936 and 1937). He was a member of the "50-Year Club" and was made an honorary member of the association in 1948.

He served in World War I and was discharged as a major in the medical corps.

Dr. Gerrish retired from the active practice of medicine in 1948 and he and Mrs. Gerrish went to Alhambra, California, to live.

Surviving are Mrs. Gerrish and two daughters, Mrs. Lyman Howe, Arlington,, California, and Mrs. Robert Heer, Riverside, California.

HENRY P. ROSENBERGER, M.D.

Dr. Henry P. Rosenberger, 58, a former member of the staff at Quain and Ramstad Clinic, Bismarck, died of injuries suffered February 27, 1955, in a head-on automobile collision.

Dr. Rosenberger had been associated with the Quain and Ramstad Clinic in Bismarck since 1934. He left Bismarck in 1949 to enter practice with his brother-in-law, Dr. Fred Bunker, in Aberdeen, South Dakota. He was an eye, ear, nose and throat specialist.

Dr. Rosenberger was born in 1896, in Muscatine, Iowa. He was graduated from the University of Iowa medical school in 1925. He interned at Miller hospital at St. Paul, Minnesota, and had one year of work at the University of Minnesota Hospital. He spent three years doing postgraduate work at the University of Vienna in Austria, and was an instructor at the postgraduate school of the University of Minnesota for eight months. He was a member of the American Academy of Nose and Throat Specialists. He was a past member of the Sixth District Medical Society, North Dakota State Medical Association and a member of the North Dakota Ophthalmology and Otolaryngology Society.

He is survived by his wife, Janet.

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The committee on medical history and necrology met in Fargo the latter part of 1954. At that time plans were formulated for the publication of a volume that will give the history of the development of medicine in North Dakota in the past twenty-five years. This volume will follow the one edited by Dr. J. Grassick in 1926—"North Dakota Medicine—Sketches and Abstracts."

Material is now being gathered to be included in such a volume. In addition to the history of the state society, there will be included a history of the organization and growth of the special medical societies that have grown up in the past twenty-five years.

E. H. Borth, M.D., Chairman

Committee on Nursing Education

Considered the outstanding accomplishment of the committee on nursing education is the proposed plan to have a North Dakota State Nurses Association booth at the North Dakota State medical meeting in Bismarck, April 30, May 1 to 3, 1955. This would be a courtesy booth, and would afford the nursing profession an opportunity to present charts, plans, problems and other activities that are so closely related to those of the medical profession. At the same time, it would afford a place for personal review and discussion of many of these topics by members of the medical and nursing profession. A similar opportunity, to the committee's

knowledge, has not been afforded in the past. It was thought that, by this means, a closer relationship between the medical and nursing profession in respect to administrative, educational, recruitment, distribution and other problems would result. This proposal for this booth (which was accepted favorably by the North Dakota State Medical Society Committee on Public Policy and the North Dakota State Nurses Association) was an outgrowth of the meeting of the committee on nursing education held in Fargo, December 11, 1954. Other topics discussed at this meeting are briefly outlined, along with action taken by the committee.

Nurse Scholarship Bill. Which, as of this date, has been signed by the Governor after having passed both houses.

The committee on legislation had already submitted their recommendations, and this committee concurred in their decision. Further, in regard to the bill, the committee expressed the opinion that the medical profession recognized there is a nursing shortage, and were in favor of ways and means of stimulating nursing education. The use of tax monies was questioned but felt that the matter of policy in this regard would have to be decided upon by the legislators themselves.

Nursing Shortage. This problem was considered as one ever present, particularly in small towns, and rural communities. Although the many aspects of this were discussed and reviewed, apparently nothing new could be added to current trends and ideas. It was recognized that this problem would continue to be of foremost importance on any business agenda of this committee.

Joint commission for the improvement of care of the patients. The makeup of this commission was explained; namely, representatives of the American Hospital Association, American Medical Association, American Nurses' Association, and the National League of Nursing Education. Some of the recommendations of this joint commission were presented. It was brought out that steps in North Dakota are now underway to form such joint commissions. At the state level, the following 3 members, representing the medical profession, and chosen from this committee were named: Dr. Amos Gilsdorf, Dickinson; Dr. Lloyd Ralston, Grand Forks; and Dr. Charles A. Arneson of Bismarck. As of this date, apparently, there has been no organizational meeting in the formation of this joint commission.

Brief summary. Topics discussed at the Allied Professional Group Meeting held in Grand Forks, September 27, 1954, attended by Dr. P. H. Woutat, North Dakota State medical society president, and Dr. Charles A. Arneson, chairman of the committee on nursing education, closed the meeting. Some of the more important subjects reviewed are as follows:

1. Need of attracting nurses to small towns with hospitals.
2. Desire of committee on nursing education to cooperate with the North Dakota State Nurses Association in mutual problems.
3. Joint commission for improvement of patient care.
4. Salaries and problems of nursing aides, practical nurses and registered nurses, and their relationships.
5. Poor response of medical professional groups to request for funds to aid North Dakota State Nurses Association enrollment committee.

This committee is looking forward to the North Dakota State medical meeting where it is hoped that discussion at the North Dakota State Nurses Association booth will bring out various policies, projects, and activities for this committee to pursue and undertake.

CHARLES A. ARNESON, M.D., Chairman

Committee on Official Publication

Herewith the report of official publications committee regarding the status of the South Dakota Journal and THE JOURNAL-LANCET.

Inasmuch as the directive of the house of delegates was rather vague and indefinite, your committee had a rather poor foundation for their investigation and report. However, both journals cooperated nicely and gave us a good prospectus; this, together with direct contact with many clinics of the state have given us a fairly good cross-section of prevailing opinion.

Queries submitted to clinics: "Have you, or any member of your group, had any difficulty, complaint or marked delay in having papers published by THE JOURNAL-LANCET?"

Three clinics have not responded—the remainder were all very favorable to a continuation of our present association with THE JOURNAL-LANCET. Many advised that THE JOURNAL-LANCET requested that they submit more papers for publication.

To my way of thinking, something is wrong when it becomes incumbent on the part of a publisher to solicit such material.

A careful, honest, comprehensive resume of facts submitted by both publishers leaves no doubt as to which journal should be chosen at this time.

There is a point or two in regard to the South Dakota Journal . Mr. John Foster, editor of the South Dakota Journal, advises that there may be a change in regard to the druggists. Also, in the event of a profit, this would be divided between the managing editors of both states.

There are many factors and problems which should be considered with the publisher, whoever he may be, before a contract is made. With that thought in mind, I have suggested to Mr. Cohen, editor of THE JOURNAL-LANCET, that he contact Dr. Woutat for a favorable time during our state meeting in Bismarck.

Your cominttee finds it necessary to bring in a divided report.

Minority report—1 member: "We have lost our identity and I would favor going along with the South Dakota Journal at present."

Majority report—Favorable to continuing with THE JOURNAL-LANCET, with several reservations, which I shall report to you before our Bismarck meeting.

P. G. ARZT, M.D., Chairman

Committee on Public Health

A meeting of the committee on public health of the North Dakota State Medical Association was held on March 9, 1955, in the office of the state health officer. The following were in attendance: Drs. R. O. Saxvik, chairman, Jamestown; C. O. McPhail, Crosby; A. F. Hammargren, Harvey; Percy Owens, Bismarck; T. Q. Benson, Grand Forks; and O. W. Johnson, Rugby.

Also in attendance were the following members of the committee on maternal and child welfare: Drs. R. E. Lucy, chairman, Jamestown; L. G. Pray, Fargo; M. M. Heffron, Bismarck; and John Gillam, Fargo.

Others already attending were: Frank E. Wheelon, M.D., district health officer, Minot; William Kitto, M.D., Minot; Donald Lawrence, M.D., city health officer, Fargo; Melvin E. Koons, chief, laboratory services, Grand Forks; Robert Fischer, Grand Forks; Lyle Limond, executive secretary, North Dakota State Medical Association, Bismarck; M. F. Peterson, superintendent of public instruction, Bismarck; Jerome H. Svore, director of public health, Bismarck; Kenneth Mosser, director, division of preventable diseases, Bismarck; Frederick Meyer,

State Department of Health, Bismarck; Bernardine Cervinski, director, division of health education, State Department of Health, Bismarck; and Vera Knickerbocker, director, division of public health nursing, State Department of Health, Bismarck.

The meeting was called for the primary purpose of reviewing the proposed plan of vaccinating approximately 30,000 first and second grade children in North Dakota. A sufficient amount of Dr. Salk's polio vaccine, in the event it is licensed by the National Institutes of Health, is to be made available to vaccinate all first and second grade children by the National Foundation for Infantile Paralysis. This vaccine, if licensed, is to be available the first part of April.

Information was presented to the committee pertaining to all phases of the program and a "Summary of National Planning Meeting on 1955 Poliomyelitis Vaccine Program" dated January 10, 1955, was reviewed. Comments from the other medical societies were read to the group.

The state health department will be the potential recipient of the vaccine and they requested a recommendation from the committee on public health and the committee on maternal and child welfare of the State Medical Association as to whether or not it was the type of project in which the medical association would be willing to participate. After reviewing all aspects of the program and realizing that this would be the only time that the National Foundation for Infantile Paralysis would be furnishing vaccine on a mass immunization basis, the committee adopted the following motion: It was moved that the committee on public health and the committee on maternal and child welfare of the state medical association approve and recommend that the polio vaccination program be carried out in the state.

R. O. Saxvik, M.D., Chairman

Committee on Public Policy and Legislation

The following is the report of the committee on public policy and legislation:

The North Dakota State Medical Association took action in the house of delegates in May 1954. First, to approve the recommendation of dividing the state into 49 legislative districts and recommend that such a plan be instituted. Such a plan has been instituted through the executive secretary's office in Bismarck, and the councillors of your society have made appointments of men in the various districts who are acquainted personally with the legislators of their own district. The function of this set-up was tried in the 1955 legislative session and worked fairly well. There are many places and things that can be done to improve the function of this set-up, and I trust the councillors will review this and make any corrections, amendments, and institutions of any phase of the work which will improve the working of such a plan.

Second, the house of delegates recommended the continuation of the medical, press, radio and TV conferences; this has been done.

Third, it recommended the inauguration of medical, public forums. This particular phase of the program needs to be expanded and carried on.

Fourth, it recommended regional series of medical, legal conferences. This is in the process of being instituted and will undoubtedly be put into active form very shortly.

Fifth, it took no action on question as to whether the state association should take an active part in the controversy concerning the establishment of a four-year medical school. Apparently the house was willing to leave this to the discretion of the committee on medical education and public policy and legislation. The house affirmed the following: The North Dakota State Medical Association has consistently pursued a conservative policy with respect to the establishment of a four-year medical school in the state. It should reaffirm its policy and inform all interested parties that it is willing and ready to cooperate in a sane appraisal of the situation and the defense of the conclusions drawn from factual data.

The committee on public policy and legislation had a combined meeting with the committee on medical education in Fargo, North Dakota, December 11, 1954. A majority of members of both committees was present. Others present were Dr. P. H. Woutat, president of the North Dakota State Medical Association; Dr. J. C. Fawcett; Dr. O. A. Sedlak; Dr. Nelson Youngs, and Mr. Lyle Limond, executive secretary. Dean T. H. Harwood, UND Medical School, gave a report on an up-to-date picture of the medical school, and Dr. Harwood stated as follows: (1) additional equipment is still arriving for expanded facilities; (2) twenty-one students have now been accepted for the 1955 freshman class; and (3) status of the third and fourth years is as follows: (a) it is out of the question for 1955 and 1956, but not for a future date; (b) development of a residency program is essential; (c) there is a possible entree through the field of rehabilitation; (d) mill levy funds are available above current needs and are being husbanded; (e) the thirty-fourth session of the legislature must be told that there will not be a four-year school by 1956. (After considerable study on this question, both within the committee on public policy and legislation itself, and also by directors of the University of North Dakota Alumni Association, these meetings being conducted separately, both groups arrived at the same conclusion; that nothing should be done relative to informing the legislature in 1955 as to progress at the medical school unless this was specifically requested by the legislators; and that no action be taken to change the status-quo of the statute as it exists); and (f) physicians' attitude is a positive one; if we have a four-year school, it must be a good one with a competent staff, good facilities, and with clinical material present, since you cannot teach medical students without hospital teaching beds.

Following this report, the committee on public policy and legislation went into a session on its own problems separate from the medical education committee. A motion was made that full support be given to Dean Harwood of the North Dakota Medical School by this committee to his education program as outlined to this committee, and his continued efforts to accomplish his goal as he and the board of higher education sees fit.

A proposed legislation of the Optometry Association, which association wishes to make some changes in the present practice act, was studied at the request of Mr. E. F. Engebretson, attorney for the optometrists. The committee felt that the language was ambiguous in the proposed change of the statute and the presesnt law is satisfactory. It was moved and seconded that the proposed legislation be referred to the North Dakota Society of Ophthalmology and Otolaryngology for study and recommendation.

The committee next studied the legislation being proposed by the division of special education of exceptional children of the department of public instruction for the coming legislative session. It was moved and seconded that the division consider the inclusion of pre-school children in speech therapy and hearing conservation.

The committee next studied the nurses scholarship bill

being sponsored by the North Dakota State Nurses Association. Further study of the bill was tabled with the stipulation that the committee aid the nurses association by suggesting that nurses get a ruling from the attorney general's office as to the proposed bill's constitutionality. It was moved and seconded that this committee disapprove the use of tax money for nursing education as well as medical education and suggests that nurses seek other revenue for raising the funds for nurse scholarships.

It would be my recommendation that the public policy and legislation committees be separated, and a separate division be set up of public policy and public relations. A division of that type should be active for twelve months out of the year, constantly, both legislative and non-legislative years. Such a committee would automatically take over the various functions which have been recommended by the house of delegates, i. e., the continuation of medical-press conferences, and the continuation of medical-legal conferences. We are aware of the fact that there is still continued effort to socialize medicine in the Capitol at Washington, and must constantly be on the alert to create a better feeling between the medical association and the public in our state. This has been discussed with our president, Dr. P. H. Woutat, and he is in accord with such a recommendation.

A number of bills were introduced in the recent legislative session and these undoubtedly have come to your attention. The bill of greatest consequence was the all-inclusive osteopathic bill, which would have given the osteopaths in the state of North Dakota an equal right as to the practice of medicine in the state of North Dakota, as it would have given to the average general practitioner. This involved major surgery and all its ramifications. This was introduced as house bill No. 834 and your chairman had occasion to appear before the house committee on this bill. Dr. Philip Woutat, president of the North Dakota State Medical Association, was also present, as was Dr. C. H. Peters, Quain and Ramstad Clinic, Bismarck. An objection was made to this bill as it was presented by the Osteopathic Association by all three representatives of the North Dakota State Medical Association and the bill was killed in committee.

Other legislation that took place, which we did not enter into on too active a basis, is as follows: SB 61, narcotic privileges and surgical chiropodists; SB 117, anti-fluoridation; SB 125, coroners to be physicians; SB 155, pharmacy bill; SB 165, pharmacy bill; SB 188, fixing of medical and hospital fees by state welfare board; HB 664, licensing of masseurs; HB 735, medical examination for teachers; HB 750, chiropractic scholarships; HB 765, pharmacy bill; HB 791, pharmacy bill; and house concurrent resolution Z (state-operated health and accident insurance system). The results on all of these bills are to be found in the report of our executive secretary.

Your chairman made an effort to assist the North Dakota State Health Department in obtaining a sufficient budget for the coming biennium by appearing before the house committee pleading for adequate funds. However, it would appear that our efforts along this line were not sufficient and the department was cut very severely with the result that there will have to be curtailment of our health program in this state to some extent for the next two years. I should hereby recommend that each and every physician in the state of North Dakota, who is dependent to a very substantial amount upon practicing good medicine only by being able to obtain services of the North Dakota State Department of Health, make special effort in coming legislative sessions to assist the department of health in the state of North Dakota to obtain sufficient funds to carry on a good public health program.

Finally, I wish to call to your attention the efforts of your executive secretary, Mr. Lyle Limond. I have had the opportunity as have several others, to watch Mr. Limond in action and can assure you that he carried the responsibilities of the medical association with good judgment and with consummated skill that left most of the legislators with a good feeling toward organized medicine. I trust that his services will be amply rewarded, both by suitable accolade and by a more generous salary, if it is possible to do so after checking our financial status.

O. W. Johnson, M.D., Chairman

It was moved by Dr. Sandmeyer and seconded by Dr. Burt, that the reports of the committee on medical economics, including the sub-committees, be referred to reference committee number five. Motion carried.

Committee on Medical Economics

I am submitting my 1954 report for the medical economics committee as follows:

The programs instigated by this committee have been functioning well and no need for a meeting of a full committee was deemed necessary during the past year. The liaison committee of the North Dakota State Medical Association, which is a sub-committee of the medical economics committee, met on August 7, 1954, with Mr. Ralph Atkins of the welfare board, and numerous items of the welfare fee schedule were discussed with him. This program has been functioning very well with a few minor exceptions. Several doctors have been charging more than the welfare fee schedule allows and it was determined that this would be corrected by personal correspondence. It was suggested by the welfare board at this meeting that a medical formulary for drugs to be used should be set up, but this committee did not believe that this was necessary, and believed that it would restrict the doctor in his care of the indigent patient. It is our recommendation that all doctors in the state adhere strictly to this welfare board fee schedule so that this program can continue to function well in the future.

Our relations with the Workmen's Compensation Bureau have been entirely satisfactory and no change in schedule or arrangement with them is contemplated.

The Veterans' Administration have changed their arrangement with us so that authorization for work now comes directly from the Veterans' Administration office in Fargo, North Dakota, rather than through our state office. They are using their own fee schedule which, from a survey, seems to be satisfactory to most of the doctors throughout the state. This fee schedule, however, has not been approved by the medical economics committee.

The Blue Cross and Blue Shield programs have, and are, in the process of re-arranging their fee schedules to make their own program more effective financially. It is the recommendation of the chairman of this committee that the Blue Cross and Blue Shield work with the medical economics committee in the establishment of a fair fee schedule to the doctor and one that will help this program to be financially solid.

Ted Keller, M.D., Chairman

Sub-Committee on Medical Prepayment Plan

Last year the house of delegates recommended that efforts be made to encourage more active participation by members of the Blue Shield Board. I am pleased at

this time to report that during the past year many difficult problems have confronted the board and that they have responded to the best of their ability to solve these matters.

Last year it was also recommended that cooperation of the sub-committee on prepayment medical care with the board of directors of the Blue Shield be obtained to resolve differences of opinion among members of the association, and among the physicians participating in the Blue Shield Plan regarding the maximum income range under which service benefits are granted Blue Shield subscribers, and regarding fee schedules. A joint meeting of the board of directors of the Blue Shield and the members of the sub-committee on prepaid medical care was held in Fargo on November 20, 1954. At this time, members of the committee had first hand information regarding the problems faced by the Blue Shield board. All members were given free discussion of the matter and when the final vote was taken, it was felt that the wishes of the majority of the profession were carried out. Whether or not the resulting lowering of the income range was a judicial move, time alone will tell.

Another meeting was held in Fargo at the time the council met on December 11th. At this time it was the intention to present the problems of the commercial underwriters. However, during the attempt to find a suitable speaker, it was discovered that the commercial companies are violently opposed to the service feature of the Blue Shield plans. They also intimated that there was a lot of abuse of prepayment plans. Cursory investigation showed that there was perhaps some truth to their allegations. Until more factual material could be obtained, it was thought prudent to call off the meeting with the commercial carriers.

It is my request, at this time, to have the sub-committee on prepayment medical care made a permanent committee. It is also by recommendation that this committee be empowered to conduct a rather thorough study to see whether or not there are abuses of prepayment plans. It is a known fact that abuses do occur, but an impartial study by this committee could easily determine the magnitude of these abuses. With this knowledge, we could sit across the table with the commercial underwriters and reach some agreement. When accusations are thrown back and forth, nothing can be accomplished.

I wish to thank the members of my committee for the way they have responded and for the suggestions they have offered. Health insurance is here to stay, and it is up to the medical profession to take the lead in making it work.

O. A. Sedlak, M.D., Charman

Committee on Rural Health

Your committee on rural health respectfully submits the following report:

The committee has held no meetings this past year. Your chairman attended the interim meeting of the council at Fargo, December 10-12, 1954. At this meeting, your chairman requested permission from the council to meet with the farm groups of the state and work out a short panel program with them when they held their yearly meeting. Your chairman's request was granted by the council.

Your chairman was unable to attend the National Rural Health meeting at Milwaukee. This meeting was attended by Dr. W. A. Wright of Williston; Dr. Leonard Larson of Bismarck; and our executive secretary, Mr. Lyle Limond of Bismarck. Dr. Wright reports the meeting well attended and a very interesting and instructive program was presented. Dr. Leonard Larson of Bismarck appeared on the program.

Your chairman has received from time to time, this past year, reports from our executive secretary on the physician's placement service. According to his report, 51 physicians have inquired about openings in our state. Three physicians have been placed through the physician's placement service. I wish to thank our executive secretary for his fine interest in this service.

Your chairman and the Grant County Health Council has worked out a questionnaire for a health survey for Grant county. This will obtain information regarding immunization, information regarding rheumatic fever, diabetes, brucellosis, tuberculosis, carcinoma, milk supply, sewage disposal, culinary water supply, etc.

This survey should be completed by the end of this coming May. Mimeograph copies will be made available of this report. Information regarding this report may be obtained from our executive secretary's office.

M. S. Jacobson, M.D., Chairman

Sub-Committee on Veterans Medical Service

The following is a report from the chairman of the sub-committee on veterans medical service to the committee on medical economics and to the house of delegates.

This agency has been in operation for 9 years, and I believe that most physicians in the state are familiar with the recent method of operation of the office located at Bismarck. A total of $27,991.75 will have been paid to the physicians in North Dakota for their services in 1954. Of this amount, $14,492.75 was for treatment, and $13,505 was paid for examinations for rating purposes.

The important change in operations, as all of you have been advised, is that, effective February 1, 1955, the office in Bismarck ceased to function as an authorizing and disbursement agency, these functions being handled directly by and from the Veterans Administration center in Fargo. At the date of this report, the Bismarck office is in the procedure of closing accounts.

The change which is now in effect was the result of a request from the Veterans Administration as an economy move. Members of this committee met with representatives of the Veterans Administration in August 1954 and members of the council were contacted at that time and the change received the official approval of the council at the December 11, 1954 meeting.

The office still has a loan of $2,500 from the State Medical Association. The contract with the Veterans Administration includes a no-profit, no-loss agreement; it is hoped that negotiations with the Veterans Administration will allow a full repayment of the $2,500 to the State Medical Association.

The present fee schedule will remain in effect and the Veterans Administration requests that the North Dakota State Medical Association continue a sub-committee on veterans medical service to act as a liaison agency to assure satisfactory operation of the new plan. The council recommended that this committee be continued.

The Veterans Administration has expressed its satisfaction with the operation as it has existed and this committee requests the continued cooperation of the physicians in the state with the Veterans Administration. Our relationship with the Veterans Administration has been very cordial and satisfactory. The committee expresses its gratitude to Mrs. Anita Meisner, who has been most efficient in her work in the office.

Robert B. Radl, M.D., Chairman

Speaker Dodds at this time established the committee on resolutions and stated that the reports for that committee would be brought up as the session progressed.

Dr. Toomey was appointed chairman of the reference committee to consider the reports of the council, councillors and special committees. Inasmuch as he was not present, Dr. Hawn was requested to serve as chairman of this committee and Dr. Schwinghamer was also appointed a member.

OLD BUSINESS

At the last session of the house of delegates a change in the constitution was approved by the delegates, but, of course, any change in the constitution must be presented at two consecutive annual sessions. The secretary was at this time requested to read the change that was proposed and passed at the last house of delegates meeting.

Secretary Boerth: A recommendation was made to increase the number of councillors from 8 to 11, having 1 delegate from the Kotana society and 1 delegate from the Traill-Steele society, and having our immediate past president act as a councillor at large, giving a total of 11 councillors, and a quorum of 6, or a majority of the 11, to constitute a quorum.

Speaker Dodds explained, by way of clarification, that this was proposed and passed at the last meeting of the house because the council has had some difficulty in times past to get a quorum together to transact business.

A motion was made by Dr. Haugrud to accept this second reading of the change in the constitution, and seconded by Dr. Craven. The motion passed.

Speaker Dodds next introduced Mrs. Dorothy Bacheller, president of the Woman's Auxiliary to the North Dakota State Medical Association, who gave a brief review of the activities of the auxiliary, as follows: "Dr. Dodds, members of the house and delegates and guests. I appreciate the privilege of reporting auxiliary progress to you and am happy to bring greetings from our 293 members.

The framework of our organization is complete, with all 10 districts having auxiliaries to their district medical societies; but we are not content. Membership is a point of emphasis in the auxiliary. We need the helping hands of new members and the financial support of their dues. We need you to help us attain our goal. Our present membership is carrying the load of the whole program, which is designed to educate ourselves on subjects related to medicine and to deliver the message to the people of our communities through participation in the programs of other organizations to which we belong.

Our national theme for this year has been "leadership in community health," and we think it is appropriate. People in our local communities are coming to depend on us for guidance in their health programs, and they accept with confidence the information we give them. We are aware that we reflect the profession in all we say and do. Therefore, we study, to be carefully informed, before expressing opinions on the problems of health and medical care. If, through our study in auxiliary work, we can give information rather than misinformation to our lay contacts, it can bring about better understanding between the medical profession and the public.

Our state theme for this year has been "know your auxiliary." This was adopted with the thought that if we, as members, had a better understanding of the tremendous potential of the auxiliary, we could make it a better and a stronger organization.

This past year our combined district auxiliaries contributed $2,339 to the sophomore medical student loan fund to bring it to a total of $7,139 raised since the origin of this fund in 1950.

We have just started creating funds for the AMEF and have only raised $41 this year, but it is hoped that as the district auxiliaries become more familiar with this project, substantial funds can be raised.

We have sponsored future nurses clubs, cooperated with local nurse recruitment programs, and have shown a number of nurse recruitment films to interested groups. We are compiling a list of nursing scholarships and nursing loan funds which are available in the state. This list will be sent to each high school.

Through the cooperation of WDAY-TV and KXJB-TV, we have sponsored two public service films: "Operation Herbert," and "Life to Save," which were produced by the A.M.A.

We are interested in distributing *Today's Health* because we know its educational and public relations value. We have sold 149 subscriptions this year.

The other aspects of our program are more difficult to evaluate. We study medical legislation; we cooperate in the civil defense program through filter center work; we have assisted in mental health and rural health programs. Many individual members have assisted in community health and philanthropic projects and fund raising drives too numerous to mention.

I realize that many of you, undoubtedly, feel that your wives belong to too many organizations, but you know the old joke about the six shipwrecked women. There were two English women, two Irish women, and two American women shipwrecked on an island. After twenty-four hours, the two English women were not speaking, the two Irish women were fighting and the two American women had organized a club; one was president and the other secretary-treasurer.

It seems to be the nature of American women to be gregarious. You have bought your wives automatic washers, dryers, and other labor-saving devices which have given them the time to take an active part in organizations. Why not see that one of these organizations is the medical auxiliary. The national auxiliary was created at the suggestion of the A.M.A., and our state auxiliary was created with the permission of the state medical association. We have an organization which is at your disposal. You have heard of the atom bomb, but did you ever hear of the "Eve" bomb? Our potential is unlimited.

Since my theme for the year has been "know your auxiliary," it is a fitting climax to have been given the privilege of addressing you. I hope I have been able to help you to know your auxiliary. Thank you."

Continuing with the matter of old business, secretary Boerth next requested Dr. Dodds to give a report from the pharmaceutical liaison committee. Dr. Dodds spoke as follows: "Those of you who were here last year, and those who read the proceedings of the house, will recall at the first meeting of the house that Mr. Trom, chairman of the committee on inter-allied professional council of the pharmaceutical association of North Dakota, appeared before the house. We did not know the content of his presentation until it was given to us. There were many things discussed; the gist of it was that he wished the house of delegates to go on record reaffirming section 8 of the Code of Medical Ethics of the A.M.A., which has to deal with the operation by any doctor of a pharmacy, or a business other than in the medical line, for profit. This was referred to the reference committee and the committee on resolutions re-

solved that the president appoint a special committee on pharmacy to meet with delegates of the pharmaceutical association to thrash this out. We had a meeting December 12, 1954, with them in Fargo. This committee was comprised of Dr. Jacobson, Dr. Nierling, Dr. Peters, and myself. The contents of this committee meeting are given to a certain extent in my report "Pharmaceutical Liaison Committee." Briefly, we made certain recommendations there which all of you can read, and which the reference committee can consider. It amounted in summary that the use of printed prescription blanks be discontinued and the disbursing of professional samples be discontinued.

Mr. Trom again communicated with us the first part of this month and wants a similar resolution to go to the house. The pharmacy committee met this morning and talked this over. The A.M.A. House of Delegates is considering changing the Code of Ethics. It was voted down at the last meeting but it is our understanding that this is again coming up at the June meeting. It was the feeling of your committee that any definite action at this time one way or the other is probably premature because we do not know where we stand in reference to the A.M.A. This is the report I have to offer. I would like to refer this report given verbally, to the referenee committee, to eonsider."

As there was no objection from the delegates, secretary Boerth referred the above to the committee to consider special committee reports, of which Dr. Hawn is chairman.

NEW BUSINESS

Speaker Dodds next proceeded to the first item under new business for the ensuing year, which was the fixing of the per capita dues. Before this was discussed, Dr. Nierling was called on, as representing the council, to express their action in going over the budget. Dr. Nierling stated that the present dues, $75 per annum, should be retained for the current year, according to the feelings of the council. The budget had been discussed at the council meeting just concluded, and amounts to $24,116. The proposed income from the dues, as they stand at the present time, is $28,800, if everyone pays. The council would recommend that the dues be retained at the present $75 for the ensuing year.

The motion was made by Dr. Vandergon, seconded by Dr. Sandmeyer, that the dues be continued at $75 per year. Motion carried.

Speaker Dodds next requested secretary Boerth to read the appointments made by the president to the nominating committee. The nominating committee is as follows: Dr. W. H. Gilsdorf, chairman; Drs. O. W. Johnson and Keith Vandergon.

Dr. Peters next reminded the house that Dr. L. W. Larson would be up for re-election to the board of trustees of the A.M.A. at the June meeting. He asked that the house of delegates endorse his election to the board of the trustees of the A.M.A. in the form of the following resolution:

RESOLUTION

Whereas, L. W. Larson, M.D., a member of the board of trustees of the American Medical Association, has, for the past several years, served his profession, his state, and nation with unsurpassed skill and dignity; and,

Whereas, Dr. L. W. Larson continues to receive the accolades from his colleagues, co-workers and friends for his frank and honest approach to the many problems that arise in medical affairs and public matters; and

Whereas, his first term of office is soon completed and election for the position is soon to be held;

Now, therefore, be it resolved: that the North Dakota State Medical Association, in unanimous accord, seek the re-election of Dr. L. W. Larson by directing this resolution of our backing and support through our state A.M.A. delegate, Dr. Willard Wright, to the proper authorities of the American Medical Association.

Speaker Dodds referred this resolution to the committee on resolutions for action at the second session of the house of delegates. Dr. Saxvik is chairman of that committee.

A discussion followed concerning the liaison committee with the North Dakota Bar Association; Dr. Peters, chairman. It was moved by Dr. Peters, seconded by Dr. Erenfeld, that this committee be maintained. Motion carried.

Dr. Melton next presented a resolution to the house of delegates, as follows:

RESOLUTION

Whereas, the National Foundation for Infantile Paralysis has led, unified, and directed the fight against poliomyelitis for over 17 years, always working through established medical and research groups; and

Whereas, large sums of money have been expended for patient care, professional educational programs, research in virology and epidemiology, and the production and testing of the trivalent vaccine developed by Dr. Jonas E. Salk; and,

Whereas, this vaccine has now scientifically been proven safe and effective and is now licensed by the National Institute of Health; and,

Whereas, the March of Dimes program is making this vaccine available to all first and second grade pupils; and,

Whereas, the team work of the medical profession and lay volunteers of the National Foundation for Infantile Paralysis is outstanding in the annals of medicine;

Now, therefore, be it resolved: that the North Dakota State Medical Association hereby commend the National Foundation for Infantile Paralysis and the thousands of North Dakota volunteers in its county chapters throughout the state for their leadership and service in helping to build a healthier world for our children, and advance the cause of preventive medicine.

This resolution was referred to committee number six, Dr. Saxvik, chairman.

Adjournment

It was moved and seconded that the first session of the house of delegates adjourn to reconvene at 2:30 P.M., Sunday afternoon.

SECOND SESSION, HOUSE OF DELEGATES

Sunday Afternoon, May 1, 1955

Bismarck, North Dakota

The second session of the House of Delegates was called to order by speaker Dodds at 2:30 P.M., May 1, 1955, in the Prince Hotel, Bismarck, North Dakota.

Dr. Haugrud, chairman of the credentials committee, reported that a quorum was present, and secretary Boerth called the roll. The following doctors were present:

William Fox, Rugby; E. J. Schwinghamer, alternate, New Rockford; E. M. Haugrud, Fargo; Frank M. Melton, Fargo; L. E. Wold, Fargo; H. W. Hawn, Fargo; R. C. Painter, Grand Forks; John Sandmeyer,, Grand Forks; F. A. Hill, Grand Forks; Bruce Boynton, Grafton; A. R. Sorenson, Minot; G. M. Hart, Minot; A. F. Hammargren, Harvey; F. R. Erenfeld, Minot; V. J. Fischer, Minot; G. Christianson, alternate, Valley City; M. S. Jacobson, Elgin; Carl Baumgartner, Bismarck; O. C. Gaebe, New Salem; C. H. Peters, Bismarck; R. O. Saxvik, Jamestown; Robert Gilliland, Dickinson; Keith Foster, Dickinson; Thomas E. Pederson, Jamestown; John Van Der Linde, Jamestown; Keith Vandergon, Portland, and J. D. Craven, Williston. There were 27 doctors answering the roll call.

The first order of business was the reading of a communication which the secretary received. Secretary Boerth read as follows: "I hereby tender my resignation as a council member from the First District Medical Society, effective immediately"; signed: Dr. O. A. Sedlak, Fargo, North Dakota. Dr. Vandergon made the motion, seconded by Dr. Sandmeyer, that Dr. Sedlak's resignation be accepted. Motion passed.

The next order of business was the selection of the meeting place for the next annual session. In 1954, the house approved the joint meeting with the South Dakota Medical Association at Aberdeen, South Dakota.

This meeting is to be June 2, 3, 4, and 5, 1956. There was a motion passed in the house a year ago that the council and the house meet in North Dakota prior to the scientific session in Aberdeen, South Dakota. The council would like the house to reconsider that motion.

Speaker Dodds introduced Dr. Fawcett, chairman of the council, to give a report of their action and recommendations. Dr. J. C. Fawcett:

"The council, as you noticed in the handbook of my report for the past year, discussed that at considerable length, and we could not see very much sense in calling two separate meetings. At that time a resolution was passed requesting further investigation of it, and suggesting that the meeting be held at the same time as the Aberdeen meeting. Yesterday, at our meeting, a formal act was taken to the effect that the council would definitely meet in Aberdeen, and we recommend that the house reconsider the action as to meeting at the same time."

Speaker Dodds stated that the council had voted to start their meeting on June 2nd and the house would have to do the same; that is, have meetings June 2nd and 3rd. The chair, at this time, entertained a motion to meet at Aberdeen, South Dakota, on June 2nd and 3rd.

This motion was made by Dr. Craven, seconded by Dr. Hawn, and carried.

The next order of business was the reading of the minutes of the first session, but it was moved by Dr. Haugrud, and seconded by Dr. Vandergon, that the reading of the minutes be dispensed with. Motion carried.

Speaker Dodds next asked for the report of the nominating committee.

Dr. W. H. Gilsdorf, as chairman of the nominating committee, submitted the following nominations: president, Dr. D. J. Halliday, Kenmare; president-elect, Dr. R. H. Waldschmidt, Bismarck; first vice-president, Dr. R. W. Rodgers, Dickinson; second vice-president, Dr. O. A. Sedlak, Fargo; speaker of the house, Dr. G. A. Dodds, Fargo; vice-speaker of the house, Dr. R. E. Leigh, Grand Forks; secretary, Dr. E. H. Boerth, Bismarck; treasurer, Dr. E. J. Larson, Jamestown; delegate to the A.M.A., Dr. Willard Wright, Williston; and alternate delegate to the A.M.A., Dr. G. W. Toomey, Devils Lake.

Councillors—Terms expiring 1958: Dr. J. C. Fawcett, Devils Lake, second district; Dr. R. D. Nierling, Jamestown, seventh district; Dr. A. R. Gilsdorf, Dickinson, ninth district; and Dr. J. D. Craven, eleventh district (Kotana district).

Term expiring 1957: Dr. Keith Vandergon, Portland, tenth district (Traill-Steele district).

Term expiring 1956: Dr. A. C. Fortney, Fargo, first district (balance of Dr. Sedlak's term).

State Board of Medical Examiners: Dr. V. J. Fischer, Minot; Dr. W. E. G. Lancaster, Fargo; and Dr. Charles Arneson, Bismarck.

State Health Council: Dr. O. W. Johnson, Rugby; and Dr. Robert Gilliland, Dickinson.

Medical Center Advisory Council: Dr. P. H. Woutat, Grand Forks.

Dr. Gilsdorf moved that the house accept these nominations unanimously. This was seconded by Dr. Pederson, and a unanimous vote was cast.

Dr. Woutat reported that he had had a phone call from Dr. Halliday, personally, inasmuch as he was unable to attend the meeting due to ill health. He sent his regrets and best wishes to the members of the association. Dr. Woutat stated that he and Mr. Limond had sent, by telegram, the proper statement from the house of delegates and the general membership, to Dr. Halliday.

REPORTS OF REFERENCE COMMITTEES

Reference Committee to Consider the Reports of the President, Secretary, Executive Secretary, and Treasurer

Dr. Jacobson, chairman, presented the following reports and their discussions, which were adopted section by section, and as a whole.

1. *Report of the President.* Your committee has reviewed the report of the president. We support the president in his opinion that the elected governing representatives of this association be active in stimulating the general membership, regarding the functions and activities of this association. In addition, we feel that his recommendation for appointment of a public relations committee be adopted. We heartily endorse continuation of attempts to place new physicians in needed rural areas, through the efforts of the executive secretary and the rural health committee.

It is our opinion that the problems concerning the Blue Shield program are particularly disturbing. Considerable initiative must be exercised by the committee on prepayment medical care during the ensuing year, or these problems will be increased. Careful selection of an active committee is mandatory.

We commend the president on initiating committees for liaison work with the state bar association and the state hospital association.

We support our president's opinion that the council and the house of delegates should meet in Aberdeen, in 1956, just prior to the joint state meeting.

In order to clarify the sections on membership of our constitution and by-laws, we concur with the recommendation for a new permanent committee on constitution and by-laws which would include the secretary and the speaker of the house.

We feel that president Woutat has performed his duties in a very outstanding manner, and deserves the gratitude of the state association.

Speaker Dodds asked the house of delegates to give the president, P. H. Woutat, M.D., a rising vote of thanks for his work with the association. The rising vote of thanks was given. This portion of the report was unanimously adopted.

2. *Report of the Secretary*: The reference committee reviewed the report of the secretary and feels that the problem of timely collection of dues is one to be solved at the local level. This portion of the report was adopted.

3. *Report of Executive Secretary*: The report of the executive secretary was reviewed and the committee found the sustained effort by our executive secretary continued. Attention was called to his comments regarding the legislative sessions and the bills introduced during the past session of the legislature. The committee feels that he is to be commended for his excellent handling of this difficult assignment. The committee suggests consideration for his thoughts for the future, and commend him for the fine job he has done. This portion of the report was adopted.

4. *Report of the Treasurer*: The report of the treasurer was carefully perused, and the committee moved that it be adopted. This portion of the report was adopted.

The motion was made by Dr. Jacobson, seconded by Dr. Pederson, that the report as a whole be adopted. Motion carried.

M. S. Jacobson, M.D., Chairman
John Sandmeyer, M.D.
R. D. Weible, M.D.
F. R. Erenfeld, M.D.

Reference Committee to Consider the Reports of the Council, Councillors, and Special Committees

Dr. Hawn, chairman, presented the following reports and their discussions, which were adopted section by section, and as a whole.

1. *Report of the Chairman of the Council:* Your reference committee has reviewed the report of the chairman of the council. It was noted that a pre-convention fund of $1,000 was set up for the present annual meeting of the North Dakota State Medical Association and concur in this allocation.

The committee discussed at some length the possibility of establishing a four-year medical school at the University of North Dakota and the committee feels that the decision reached by the council to accept the proposals as outlined by Dean Harwood should be followed.

The committee noted that the council had been advised that the physicians draft law would expire in June, but that selective service will still demand the men graduating from school, unless deferred because of residency. Availability of local practicing physicians would be determined by the local draft boards.

The reference committee noted with pleasure that the council recommends that the annual meetings of the council and the house of delegates should be held in Aberdeen just prior to the joint meeting of the two associations in June 1956.

It was moved by Dr. Hawn and seconded by Dr. Boynton, that this portion of the report be adopted. Motion carried.

2. *Reports of the Councillors*: The reference committee reviewed the various reports of the councillors and commended the members of the association on the number and caliber of the meetings that have been held during the past year. This portion of the report was adopted.

3. *Report of the Committee on American Medical Education*: The reference committee reviewed the report of the committee on American medical education, and wishes to add their voices to that of the chairman that all of us support our medical schools in a financial way. This portion of the report was adopted.

4. *Report of the Committee on Emergency Medical Service*: This report was reviewed and the committee agreed with the recommendations that this association form a plan with some modifications from that adopted by the state of Oregon. The committee also concurs with the further recommendations of the chairman of this committee. This portion of the report was adopted.

5. *Report of the Committee on Diabetes:* The reference committee reviewed the report of the committee on diabetes and noted with regret that so few centers are holding Diabtic Detection Week in their communities. The chairman of this committee was particularly commended for his unfailing zeal in carrying out the drives for the detection of diabetes. This portion of the report was adopted.

6. *Report of the Committee on Displaced Physicians*: The committee discussed at some length the report of the chairman of the committee on displaced physicians and are quite sympathetic to the problems involved. Your committee feels that the problem of the displaced physician in North Dakota is one that requires considerable attention from all the members of this association. We wish to go on record as concurring in the recommendation of the chairman that we continue to provide a plan fair to the graduates of the United States medical schools and to carefully select competent foreign graduates, as well as to exclude those who are unfit to practice medicine. This portion of the report was adopted.

7. *Report of the Committee on Mental Health:* The reference committee reviewed the report of the chairman of the committee on mental health, and agrees with the recommendations carried in that report. This portion of the report was adopted.

8. *Report of the Pharmaceutical Liaison Committee:* The report was reviewed by the committee and, after considerable discussion, it was agreed that no definite motion be taken at this time relative to the ethics of drug dispensing or financial interests in pharmacies by physicians. It is recommended that every effort be made to follow the specific recommendations of the committee relative to dispensing professional samples, and suitable prescription blanks. This portion of the report was adopted.

The motion was made by Dr. Hawn, seconded by Dr. Craven, that the report as a whole be adopted. Motion carried and the report as a whole was adopted.

H. W. Hawn, M.D., Chairman
Bruce Boynton, M.D.
Robert Gilliland, M.D.
E. J. Schwinghamer, M.D.

Reference Committee to Consider the Reports of the Delegate to the A.M.A., Medical Center Advisory Council, and the Committee on Medical Education

Dr. Peters, chairman, presented the following reports and their discussions, which were adopted section by section, and as a whole.

1. The reference committee reviewed the report of the delegate to the American Medical Association and complimented him on the summary of his activities and of some of the major problems confronting the American Medical Association.

It was recommended that consideration be given to his suggestion that the expenses of the alternate delegate to the American Medical Association be paid, to attend one of the sessions of the house of delegates. This portion of the report was adopted.

2. The committee reviewed the report of Dr. L. W. Larson, the representative of the Medical Center Advisory Council, and his summation of the problems of the advisory council. They heartily endorse his recommendations that: (a) the North Dakota State Medical Association continue its support of a realistic approach to the problem of expansion of the present two-year medical school to a four-year accredited institution; and (b) that physicians throughout the state of North Dakota be urged to encourage eligible boys and girls to apply for admission to the North Dakota Medical School. This portion of the report was adopted.

3. The reference committee, in reviewing the report of Dean Harwood, wishes to commend him for the summary of the problems that now exist.

It is felt that the recommendations of the secretary of the Association of American Medical Colleges should be carefully followed in implementing any plans for a four-year school. It is also felt that the development of internships and residency programs should be encouraged to meet the need for North Dakota physicians.

The committee took note of the recommendation that a rehabilitation center be set up at Grand Forks. Further discussion and investigation is required. It is granted that such a center would contribute to the development of the university, but we question its general availability to the population of the state.

The reference committee commended Dean Harwood and the Committee on Medical Education for their intensive efforts in developing a sound and practical med-

ical educational program for North Dakota. This portion of the report was adopted.

It was moved by Dr. Peters, seconded by Dr. Hangrud, that this report as a whole be adopted. Motion carried.

C. H. Peters, M.D., Chairman
L. E. Wold, M.D.
Keith Foster, M.D.

Reference Committee to Consider the Reports of the Standing Committees

Dr. Sorenson, chairman, presented the following reports and their discussions, which were adopted section by section, and as a whole.

1. The reference committee reviewed the report of the committee on cancer and complimented this committee and its chairman, Dr. Lund, on the excellent presentation and scope of its committee's work during the past year. It has required the sacrifice of a great deal of time and labor to present the cancer caravan program throughout the state. The committee suggested that a copy of this report be made available to every doctor in the state of North Dakota. It was suggested that a special vote of thanks be given to Dr. Lund and his cancer committee. This portion of the report was adopted.

Speaker Dodds at this time requested Mr. Limond, executive secretary, to take care of the recommendation that Dr. Lund's report be mailed to every member of the Association.

2. The committee reviewed the report of the committee on crippled children and wished to emphasize the following points: (a) the recommendation of the state medical association to make an attempt to secure funds from benevolent organizations for children suffering from rheumatic heart disease, epilepsy and possibly other crippling conditions; (b) more education be given the public regarding various crippling conditions through the media of TV, radio, and the public forum; and (c) the recommendation that a paper on epilepsy and its treatment be given every few years at the annual meeting of the North Dakota State Medical Association as part of its program as a means of informing the profession more adequately concerning this disease. This portion of the report was adopted.

3. The reference committee reviewed the report of the committee on industrial health and trauma, and moved its adoption. This portion of the report was adopted.

4. The reference committee reviewed the report of the committee on maternal and child welfare. The committee has a plan regarding a proposed maternal mortality survey, accepted and approved by the North Dakota Society of Obstetrics and Gynecology, and recommends that this also be adopted by the North Dakota State Medical Association. The reference committee feels that some clarification of the program submitted should be given to the house before it is acted upon. It is suggested that some informed person of this committee take the plan, point by point, and clarify its meaning. This portion of the report was adopted.

Speaker Dodds declared the subject open for discussion, and called on Dr. Saxvik, who spoke as follows:

"I cannot shed too much light on the specific questions raised. This proposal has been up for at least four years. The committee has asked the health department to assist this in a financial way. It is my understanding, from Dr. Lucy, that the total arrangement for the survey endeavor, or the coordinators, could be arranged through the committee of the North Dakota Society of Obstetrics and Gynecology. We felt, in the health department, that this should be kept strictly as a professional procedure."

Speaker Dodds:

"Dr. Gillam spoke to me about this a year ago. This program was approved and the council voted $100 to implement the development of the program. The committee did not use the $100. It is my understanding that this is on a national level. That is, the obstetric societies are proposing this on a national scale."

Dr. Nierling:

"I talked to Dr. Lucy about this on different occasions. I am not on this committee. They plan on modeling this after a similar survey made in Minnesota. This is to be of help to the doctors in cases of maternal and child mortality. I think the report was to be rendered to the State Society of Obstetrics and Gynecology. In Minnesota, they presented a discussion of these findings in one of the courses at the university and this was a very interesting program."

Dr. Boynton:

"Four years ago I was practicing in Minnesota. I am somewhat familiar with this survey. I believe there were only two investigators and these two men were very skillful in getting information. No doctor could go through an experience like that without wishing to know where he had made a mistake and to try to correct some of the mistakes. I believe our only question here, today, is how we should implement this progrm. We should not put this off. We could designate how they are to pick these investigators. I believe the group in Minnesota was a continuing group and this survey has diminished the numher of maternal deaths very appreciably in the state of Minnesota."

Speaker Dodds:

"Dr. Boynton, would you wish to offer part of that in the form of an amendment to this motion; that is, that the men appointed as investigators, or consultants, should be obstetricians, or fifty per cent of their practice should he devoted to obstetrics or pediatrics?"

Dr. Boynton:

"I believe pediatrics is unrelated here. Perhaps this committee should consist of 5 men; at least half of the practice of each man should consist of obstetrics and gynecology work. I would like to move that the president of our association be empowered to pick these 5 men and that 50 per cent of their practice be obstetrics and gynecology."

The amendment offered by Dr. Boynton was seconded by Dr. Van Der Linde.

Dr. Sorenson:

"We were wondering whether the State Medical Association would want to put their stamp of approval on this before it was planned out?"

Speaker Dodds asked for any discussion of the amendment and Dr. Woutat responded:

"As I interpret Dr. Boynton's motion, he would like to have the president of the State Medical Association appoint these examiners. If this had heen in effect this past year, I, as president, would have been considerably embarrassed if I would have had to appoint these inspectors. I would not have been able to. I would much prefer to have left this in the hands of the North Dakota Society of Obstetrics and Gynecology, and the committee on maternal and child welfare, where it has been. We instructed our state committee a year ago, with that in mind, at the request of the Society of Obstetrics and Gynecology. They asked for our permission, and our committee on maternal and child welfare was to work with the society on this plan. It might put the president in an embarrassing position if you ask him to select the examiners."

Dr. Baumgartner:

"I do not believe the North Dakota Society of Obstetrics and Gynecology had any intention except for us to accept their plan to go on with this mortality survey. We had it all planned out and it is just a matter of approval by the State Medical Association. I think they are capable of taking care of this program."

Dr. Boynton withdrew his motion and Dr. Van Der Linde withdrew the second made to the motion.

Dr. Melton made a motion, as follows:

"I would make a motion that the North Dakota Society of Obstetrics and Gynecology submit a concrete plan for adoption at the next annual session of the house of delegates."

This motion was seconded by Dr. Erenfeld.

Dr. Saxvik:

"I think it would be a shame to put this off for another year. Arrangements have been made for the financing of this plan. The plan has been approved by the North Dakota Society of Obstetrics and Gynecology. I know Dr. Lucy would be extremely disappointed and also the members of this committee if this were put off for another year."

Speaker Dodds:

"It would seem to the chair that possibly the details of the plan that are known to a cetrain extent might be brought out in the form of a motion here in the house, so if it is the wish of your members, the program could be put in force this ensuing year. We still have the motion that the plan he delayed for a year before it is acted on. Do you wish to delay the implementing of this plan for one year, having the committee on maternal and child welfare present the plan next year in detail at the next annual meeting in 1956? Signify by saying Aye. Opposed? Motion is defeated."

Dr. Sandmeyer:

"Would it be possible to have the committee on maternal and child welfare get in touch with the committee from the Obstetrics and Gynecology Society to work out some arrangement so that we could get the details of this plan and it would not be delayed a year?"

Speaker Dodds:

"I do not know how you are going to get the details of the plan so that you can give your approval to this when there are no members of the committee here, and this is the last meeting of the year."

Dr. Woutat:

"You can turn this over to the council at their interim meeting in the fall. It may be better than delaying this for a full year. I do not like to see this delayed for a year. We appropriated money for this committee to carry out their plans."

Speaker Dodds:

"The suggestion of Dr. Woutat's seems a good one. The chair will entertain a motion to the effect that the house approve the action of the committee on maternal and child welfare, and that their implementing the plan and their final putting it into effect would he referred to the council at their next meeting for final action. That way, you would have protection of your interests.

We have not adopted this report, and we will have to do so hefore going on with the additional business hefore this house this afternoon. What is your pleasure at this point?"

It was moved by Dr. Erenfeld, seconded by Dr. Hill, that the report as presented be adopted. Motion earried and the report was adopted.

5. The referenee eommittee reviewed the report of the eommittee on neerology and medical history and noted that 10 members have passed from the ranks of medieine. These men laid the foundation for the excellent type of medieine in North Dakota, and we wish to pay tribute to them by a moment of silenee.

This report was followed by the house of delegates standing for a moment of silenee with reverenee and respeet to these members who have passed away this past year. This adopts this portion of the report.

6. *Report of the Committee on Official Publication.* This report was reviewed by the reference committee and they noted that this eommittee presents the pros and eons of eontinuing the present arrangement with The Journal-Lancet. They brought in a divided report, the majority in favor of approving the eontract with The Journal-Lancet, and one opposed. This portion of the report was adopted.

7. *Report of the Committee on Nursing Education*: This report was reviewed by the referenee eommittee who heartily endorses the eommittee's reeommendations, to wit: that as many doctors as possible visit the booth of the North Dakota State Nurses Association at the seientific exhibit and visit with the attendants. This portion of the report was adopted.

8. *Report of the Committee on Public Health*: The reference committee reviewed this report and notes the well-attended meeting of this eommittee on March 9, 1955, held in Bismarek. The following motion was made at this meeting that the committee on publie health and the eommittee on maternal and ehild welfare approve and recommend that the polio vaccination program be earried out in the state. This portion of the report was adopted.

9. *Report of the Committee on Public Policy and Legislation*: This report was reviewed carefully as it was a lengthy and complete report of their aetivities. There are several recommendations to be acted upon by the house of delegates. It was suggested that the chairman of this committee, or some member of the committee, appear before the house and give these recommendations.

Speaker Dodds:

"Does your committee wish to make a motion to that effect at this time?"

Dr. Sorenson:

"We did not consider that because we thought it would he well for this group to hear why this committee thought the committee should be suhdivided."

Dr. O. W. Johnson:

"During a legislative year, the problems that come up are being thrown at one so rapidly there is no possibility of keeping alive the public relations. During that year, public relations have to go into the background, and there is a tendency to let them lie. Actually, puhlic relations come to the foreground during the legislative year, and your legislative committee is so husy at that time they cannot do anything about public relations. If these committees were split, one to take care of public relations and one to take care of legislation, we feel it would work much hetter."

Dr. Sorenson:

"The reference committee made the statement that this committee should he suhdivided, and, if we adopt this report, will that separate the 2 committees without any further action?"

Speaker Dodds:

"They will approve the recommendation of that report, and it would seem that would implement the introduction of two separate committees."

Dr. Johnson stated that he did not feel that any aetion need be taken. The report of the president was adopted and it was he that made the recommendation. This portion of the report was adopted.

It was moved by Dr. Sorenson, seconded by Dr. Sandmeyer, that the report as a whole be adopted. Motion earried.

A. R. Sorenson, M.D., Chairman
R. C. Painter, M.D.
Thomas Pederson, M.D.
Frank Melton, M.D.
John Van Der Linde, M.D.
C. J. Klein, M.D.

Reference Committee to Consider the Reports of the Committee on Medical Economics, Including Sub-Committees

Dr. Hammargren, chairman, presented the following reports and their diseusisons, which were adopted section by section, and as a whole.

1. *Report of the Committee on Medical Economics*: The reference committee reviewed this report and agrees with their reeommendation that all doctors in the state aeeept the fee schedule as set by the state welfare board. They agreed, with the committee, that each doctor should use drugs of his ehoiee as deemed neeessary. This portion of the report was adopted.

2. *Report of the Sub-Committee on Prepayment Medical Care*: This report was reviewed and the eommittee found it gratifying to observe that there was increased eooperation and participation between this sub-committee and the board of directors of Blue Shield.

In view of the increasing growth of prepayment medieal plans, it is felt that there should be established a permanent eommittee on prepayment medieal eare, as requested by the sub-committee. The purpose of this committee should be to eontinue the study of the use and abuse of all prepayment medieal plans, and to study the feasibility of establishing a Seal of Approval on sueh plans. The referenee committee feels that physicians should take a more aetive interest in all prepayment medieal plans. This portion of the report was adopted.

3. *Report of the Sub-Committee on Veterans Medical Service*: The committee reviewed this report and were pleased to note that the veterans medical service has functioned well over the past nine years. They commended the sub-committee, and in particular, Dr. Radl, as its chairman, for their excellent work. The committee also noted and concurred with the expression of gratitude to Mrs. Anita Meisner, for her efficient service.

It is noted that the authorizing and disbursement agency is now being handled directly from Fargo. In accordance with the wishes of the Veterans Administration and the council, the reference committee recommends that the sub-committee on veterans medical service be continued. This portion of the report was adopted.

4. *Report of the Committee on Rural Health*: The reference committee reviewed the report of the committee on rural health, and noted that the council has granted permission for the committee to set up short panel programs with the farm groups of the state. The reference committee believes that such activity should be encouraged for the betterment of public relations.

It was noted that out of 51 inquiries to the physicians placement service, only 3 physicians did locate in the state. This, again, illustrates the difficulty of placing physicians in rural communities. This portion of the report was adopted.

It was moved by Dr. Hammargren, seconded by Dr. Kohlmeyer, that the report as a whole be adopted. Motion carried.

A. F. Hammargren, M.D., Chairman
William Fox, M.D.
G. M. Hart, M.D.
F. A. Hill, M.D.
Carl Baumgartner, M.D.
A. C. Kohlmeyer, M.D.

Reference Committee on Resolutions

Dr. Saxvik, chairman of the committee, presented the following resolutions:

RESOLUTION

Whereas, the sixty-eighth annual meeting of the association held in the city of Bismarck has enjoyed the hospitality and the sunshine typical of this capital city; and,

Whereas, Mayo Evan Lips and his associates, the press and radio, the hotels and businessmen have made this session one long to be remembered;

Now, therefore, be it resolved; that the house of delegates express their appreciation by directing a copy of this resolution to the Honorable Mayor. This resolution was adopted.

RESOLUTION

Whereas, the National Foundation for Infantile Paralysis has led, unified, and directed the fight against poliomyelitis for over 17 years; always working through established medical and research groups; and

Whereas, large sums of money have been expended for patient care, professional educational programs, research in virology and epidemiology, and the production and testing of the trivalent vaccine developed by Dr. Jonas E. Salk; and

Whereas, this vaccine has now scientifically been proven safe and effective and is now licensed by the National Institute of Health; and

Whereas, the March of Dimes program is making this vaccine available to all first and second grade pupils; and

Whereas, the team work of the medical profession and lay volunteers for the National Foundation for Infantile Paralysis is outstanding in the annals of medicine;

Now, therefore, be it resolved: that the North Dakota State Medical Association hereby commend the National Foundation for Infantile Paralysis and the thousands of North Dakota volunteers in its county chapters throughout the state for their leadership and service in helping to build a healthier world for our children, and advance the cause of preventive medicine. This resolution was adopted.

RESOLUTION

Whereas, a review committee of the North Dakota Blue Shield board of directors appointed to study the problem of unnecessary use and abuse of the Blue Shield contract has found evidence of such use and abuse, especially for medical in-hospital cases; and

Whereas, this condition exists elsewhere throughout the United States; and

Whereas, unnecessary utilization of medical care plans threatens their solvency and is detrimental to the subscribers and physicians alike;

Now, therefore, be it resolved: that the North Dakota State Medical Association take official recognition of this problem and that the council take appropriate steps in cooperation with other interested agencies to inform the medical profession and the public that unnecessary use of medical care plan contracts can only result in increased premiums or insolvency of the plans. This resolution was adopted.

RESOLUTION

Whereas, L. W. Larson, M.D., a member of the board of trustees of the American Medical Association, has for the past several years served his profession, his state and nation with unsurpassed skill and dignity; and

Whereas, Dr. L. W. Larson continues to receive the accolades from his colleagues, co-workers, and friends for his frank and honest approach to the many problems that arise in medical affairs and public matters; and

Whereas, his first term of office is soon completed and elections for the position are soon to be held;

Now, therefore, be it resolved: that the North Daokta State Medical Association, in unanimous accord, seek the re-election of Dr. L. W. Larson by directing this resolution of our backing and support through our state A.M.A. delegate, Dr. Willard Wright, to the proper authorities of the American Medical Association. This resolution was adopted.

RESOLUTION

Whereas, the committee of the North Dakota Bar Association in cooperation with the special committee with your state association have met, and the mutual problems of these associations considered; and

Whereas, it is recognized that closer cooperation is desirable in the conduct of the ethics of our respective associations; and

Whereas, cooperation between the physician and the attorney is mutually desirable in the successful conclusions of each case; and

Whereas, such cooperation would expedite the work of each profession and conserve the physician's time and efforts; and

Whereas, there are no fee schedules established in the state of North Dakota for expert testimony;

Now, therefore, be it resolved: that the district councillors arrange a meeting in each of the medical districts for the purpose of discussing the mutual problems of the medical and legal professions; and

Be it further resolved: that the president of this association consider the unification of the special har committee on professional cooperation, with other committees dealing with allied professional groups; and

Be it further resolved: that the medical economics committee be designated as the liaison committee to discuss the possibilities of establishing expert testimony fee schedules.

This resolution was adopted.

RESOLUTION

Whereas, the Woman's Auxiliary of the North Dakota State Medical Association has increased its membership to 293 members; and

Whereas, the Woman's Auxiliary has taken an active leadership in community health and education; and

Whereas, the student loan fund for medical students of the school of medicine at the University of North Dakota has been markedly increased by monies from the Woman's Auxiliary; and

Whereas, the cause of medicine has been bolstered by the auxiliary development of future nurses' clubs, public service films and the promotion of the magazine "Today's Health";

Now, therefore, be it resolved: that the North Dakota State Medical Association commend the Woman's Auxiliary for their wonderful and valuable work; and

Be it further resolved: that the North Dakota State Medical Association give the Woman's Auxiliary all moral and financial aid possible in strengthening their membership and implementing their programs; and

Be it further resolved: that a copy of this resolution he directed to the president of the Woman's Auxiliary. This resolution was adopted.

RESOLUTION

Whereas, the sixty-eighth meeting of the North Dakota State Medical Association has thoroughly enjoyed and profited by the scientific program developed by Dr. C. H. Peters, chairman, and the state committee on scientific program; and

Whereas, the host, the Sixth District Medical Society, with Dr. Robert Nuessle, general chairman, has excelled in providing the membership of the association with the niceties of a gracious convention;

Now, therefore, be it resolved: that the assembled delegates demonstrate their appreciation by a rising vote of thanks. This resolution was adopted by a rising vote of thanks from the house of delegates.

R. O. Saxvik, M.D., Chairman
V. J. Fischer, M.D.
J. D. Craven, M.D.

There being no further business to bring before the house of delegates, the speaker of the house, Dr. Dodds, entertained a motion to adjourn. The motion to adjourn was made by Dr. Boynton, seconded by Dr. Hawn. Speaker Dodds declared the session adjourned sine die.

SCIENTIFIC PROGRAM

Monday, May 2, 1955
Bismarck City Auditorium

8:30 to 9:30 a.m.—Registration: Exhibit Hall on main floor—Memorial Building.
9:00 to 9:30 a.m.—Scientific film: "Visible Mouth Lesions."
9:30 to 9:40 a.m.—Greetings: Dr. P. H. Woutat, president of the North Dakota State Medical Association; Evan Lips, mayor of Bismarck.
9:40 to 10:10 a.m.—"Facilities at the Jamestown State Hospital"—Dr. John G. Freeman, Jamestown.
10:10 to 10:30 a.m.—Intermission.
10:30 to 11:00 a.m.—"Neurosurgical Procedures for the Relief of Pain"—Dr. William T. Peyton, Minneapolis.
11:00 to 11:30 a.m.—"Selection of Cases for Armchair Treatment of Coronary Thromhosis"—Dr. Ford K. Hick, Chicago.
11:30 to 12:00 a.m.—"The Choice of Treatment in Hyperthyroidism"—Dr. Perry McCullagh, Cleveland.
1:00 to 1:30 p.m.—Scientific film—"Gout and Gouty Arthritis."
1:30 to 2:30 p.m.—"Pensions for Self-Employed Physicians"—Frank Dickinson, Ph.D., American Medical Association, Chicago.
2:30 to 3:00 p.m.—"The Diagnosis and Treatment of Occlusive Abdominal Aortic Disease and Abdominal Aortic and Popliteal Aneurysms"—Dr. Walter F. Kvale, Mayo Clinic, Rochester.
3:00 to 3:30 p.m.—Intermission.
3:30 to 4:00 p.m.—"Current Accomplishments in the Bowel Obstruction Prohlem"—Dr. Owen H. Wangensteen, Minneapolis.
4:00 to 5:00 p.m.—Panel discussion: "Treatment of Hypertension"—Drs. Walter F. Kvale, Rochester; Ford K. Hick, Chicago; and William T. Peyton, Minneapolis.
6:30 p.m.—Special society dinner meetings.

Tuesday, May 3
Bismarck City Auditorium

8:30 to 9:00 a.m.—Scientific film: "Injuries of the Peripheral Nerves."
9:00 to 9:30 a.m.—"Masked Sinusitis"—Dr. Charles B. Porter, Grand Forks.
9:30 to 10:00 a.m.—"The Care of Premature Infants"—Dr. M. H. Poindexter, Fargo.
10:00 to 10:30 a.m.—"Psychiatric Aspects of Dysmenorrhea"—Dr. Irving C. Bernstein, Minneapolis.
10:30 to 11:00 a.m.—Exhibit time.
11:00 to 11:30 a.m.—"Certain Aspects of Carcinoma of the Stomach"—Dr. M. B. Dockerty, Rochester, Minn.
11:30 to 12:00 noon—"Use and Abuse of Fluoroscopy"—Dr. Laurence L. Robbins, Boston.
1:00 to 1:30 p.m.—Scientific film: "Principles of Fracture Reductions."
1:30 to 2:30 p.m.—Farewell comments: Dr. P. H. Woutat, President, North Dakota State Medical Association. Introduction: "50 Year Club" members and honorary members. Inaugural address: Dr. D. J. Halliday, president-elect, North Dakota State Medical Association.
2:30 to 3:00 p.m.—"The Avoidance and Treatment of Postoperative Lung Complicaitons"—Dr. Francis M. Woods, Brookline, Massachusetts.
3:00 to 3:30 p.m.—Intermission.
3:30 to 4:00 p.m.—"Some Misconceptions About the Eyes"—Dr. Malcolm A. McCannel, Minneapolis.
4:00 to 5:00 p.m.—Panel discussion: "Carcinoma of the Lung"—Drs. Francis M. Woods, Brookline, Massachusetts; Laurence L. Robbins, Boston; and M. B. Dockerty, Rochester, Minnesota.

PRESIDENTIAL ADDRESS

P. H. Woutat, M.D.

Reading of the lay press, the Journal of the American Medical Association, and the reports of the Washington office of the American Medical Association, cannot fail to impress one with the multiplicity of problems confronting organized medicine. Since the peaceful days prior to the early 1930's, the interest of the nation in health matters has grown to remarkable proportions. It seems to extend from the lowliest citizen on up into our governing bodies. It manifests itself in many ways, but seems to culminate in the introduction of increasing numbers of bills with medical implications into state legislatures and the congress. A total of 407 bills, containing items of medical importance, were introduced into the eighty-third Congress, and in North Dakota 15 bills of major or minor medical importance were introduced into the 1955 legislative session. Obviously, constant work is required of the legislative committee and Washington office of the American Medical Association, and periodic intensive work by state association committees and offices, to assure proper consideration and avoid passage of unwise legislation.

Organized medicine has been accused of being obstructionist to all social legislation. Of the 15 major medical bills passed by the eighty-third Congress, the American Medical Association supported 11, opposed 2, and took no stand on 2. They also supported 2 not acted upon. This is hardly a record of obstruction. The public and our legislators must understand that, both as a profession and as citizens, we have supported that which we consider good and opposed that which we consider unwise or wasteful, and that we intend to so continue.

From the report of the "Medical Task Force" of the Hoover Commission, the facts that federal expense for various medical programs and compensations now totals $4,100,000,000 a year, and includes whole or part medical care for some 30,000,000 people, gives some idea of the extent of government activity in medical fields, and no doubt gives considerable comfort to the socializers. This report also reveals many other startling facts and figures to the public and the congress. The recommendations contained therein, to quote one editorial writer, "make so much sense in the curbing of waste and extravagance that a difficult time for them on Capitol Hill seems assured." Already it appears that some of the recommendations will not be acceptable to the commission itself.

Our controversy with the Veterans Administration and some veterans' organizations appears destined to continue. Much of the publicity given to this controversy has been incomplete and distorted. The leading role of organized medicine in raising the standards of care in veterans hospitals has been forgotten. The facts that both organized medicine and individual physicians have always insisted on the best possible medical care for service connected disabilities, have approved the care of tuberculous and mental patients in veterans hospitals until local facilities are adequate, and that the only controversy lies in the field of non-service connected disabilities, have received inadequate emphasis and, at times, willful distortion.

The revelations of this same task force that 65 to 85 per cent of the patients in veterans hospitals are there for treatment of non-service connected conditions, that many beds in these hospitals lie empty, and that enforcement of ability to pay regulations has been extremely lax, have been known to the medical profession for years. It will be interesting to observe whether the presentation of such findings to the public and to congress will result in reforms, and stop the construction of more unnecessary hospitals.

We can be quite sure that the great majority of veterans have no thought that their non-service connected disabilities should be treated at government expense.

We can be equally sure that they have little realization of the extent of such treatment, or of the activities of some veterans organizations toward this end. Well-informed individual physicians can do much to give the people the facts, and present the true position of organized medicine in this controversy.

It has been estimated that at the end of 1954 over 100,000,000 people in the nation had some form of insurance against hospital expense; over 85,000,000 against surgical expense; and, over 65,000,000 against medical expense in hospitals. This is ample proof that the people have accepted the voluntary method of protection against these expenses, and are willing to pay for it. While the fantastic spread of this type of insurance is a marvelous thing, it has brought many problems as well as a serious challenge.

After the initial growing pains, and while coverage was limited to predictable items such as surgical and obstetrical care and ordinary hospital expense, things went quite smoothly. As the plans began to extend into the unpredictable fields of diagnostic and medical care, expense difficulties arose, and continue to do so as wider coverage is attempted. The inclusion of diagnostic and medical care coverage, if done on a hospital patient, has resulted in hospitalization for many diagnostic procedures that could, and should, be done in the doctor's office or as a hospital outpatient, and for treatment of many illnesses that might well be treated without hospitalization. As would be expected, the result has been financial difficulties, continually increasing premiums, and criticism from many policyholders, hospitals, and physicians.

We are frequently reminded that it is the doctor who sends the patient to the hospital, orders what is to be done, and decides the time of discharge. So, some insist, the doctors can easily police the policies and eliminate these abuses. To some extent this is possible, but unfortunately it is not that simple. Pressure from patients and, too often, from those selling the policies, frequently puts the doctor in a position that makes it impossible for him to refuse hospitalization. As long as full coverage for many minor items and diagnostic procedures is included in these policies, many people are going to try to collect, and the doctor cannot police them.

It would seem that enough experience has been obtained that we might pause and take a long look at the whole program. As originally conceived, it was designed to help people with low income to pay for necessary hospital and medical-surgical expense. As it is developing, it is showing signs of trying to do too much for too many, and is getting into trouble doing it. Very few people who can afford this type of insurance need protection against small items, yet examination of policies shows that most of them include many such items, as well as clauses that encourage hospitalization to allow payment. It seems that we are now in what, to me, is the ridiculous position of urging people to protect themselves against things they don't need protection against, and asking them to pay overhead costs.

It appears to me that we are approaching a crossroad with at least two courses. One is to continue to expand coverage until the policies cover everything, wherever it is done. This has been tried in some foreign countries, and in some places in our own, and found insupportably expensive. With no curbs, many policyholders have always made excessive demands that could not be met and still keep premiums at a reasonable level. Restraints are essential to keep the plans solvent, and to protect the reasonable policyholder from those who make excessive demands.

Another course, and probably the most encouraging to date, involves staying somewhere near to insurance principles by writing policies containing deductible and coinsurance features, at least for unpredictable items, and containing the catastrophe protection so many people need. In advocating such policies, we are told that people are demanding full coverage. This may be true where the employer pays all or most of the premium. Certainly, large segments of our population would get very interested in such policies if their real needs were considered, and the premium savings adequately discussed. Fortunately, both Blue Shield and Blue Cross, and insurance companies are finally progressing along such lines.

As physicians, we have a great stake in the continued success of this type of insurance. Its rapid growth has been one of the biggest blocks to the more complete socialization of medicine in this country. It is well indicated in history that men seeking power attempt to control or destroy that which blocks them. This, the administration's reinsurance proposal, and the supreme court's ruling that the government may regulate that which it subsidizes, must be considered together. It is highly important that both commerical insurance, and Blue Cross-Blue Shield, be allowed to develop unhampered by the threat of government interference. Both are needed, and it will be a sad event if either the insurance companies or Blue Cross-Blue Shield are forced out of this field, or if they are forced to accept government aid.

As physicians, it is partly our responsibility to see that the quality of coverage is satisfactory, that usage is not abused, that our patients are educated to the dangers of excessive demands, that they consider their real needs when purchasing this type of insurance, and that the Congress keeps the government out of this business.

The 1953 survey of the governor's state health planning committee indicates a striking improvement in medical facilities in North Dakota since 1945. In that year there were only 269 physicians in the state. In 1953, there were 442. The records of the state medical association indicated that in 1955 there are 474, an increase of 205, or 80 per cent, since 1945. Allowing for those retired and in teaching positions, we have approximately one practicing physician for every 1400 people in the state. The availability of specialist services has also increased strikingly, and those services are strategically located. Actually, there are now few conditions for which competent treatment cannot be obtained within the state.

We still have a few wide areas without a resident physician, and quite a number where additional physicians would be advisable. The report of the state health planning committee reveals that, in 1953, about 60 per cent of the physicians in the smaller towns were 50 to 60 years of age. Thus it is important that we try to convince medical students and young physicians of the advantages and opportunities of practice in our smaller communities, and that we continue our efforts to bring contact between these communities and young doctors seeking locations.

This same committee report, and the most recent figures from the state department of health concerning our hospital construction program, indicate that the number of general hospital beds in the state closely approaches 5.0 per 1000 population. These figures indicate that further expansion of general hospital facilities should be scrutinized rather closely. Communities contemplating hospital programs should study their needs carefully, and review the experience of similar hospitals in other

communities before proceeding. Future efforts should probably be directed toward modernizing and raising the standards of many of our present hospital beds, increasing nursing home type facilities, either in conjunction with present hospitals or as separate establishments, increasing our provisions for rehabilitation, and improving and expanding our mental health facilities. Decisions on these matters must be made with full cooperation between the medical profession, the State Department of Health, and interested non-medical groups.

The foregoing has touched but a few of our problems. Dr. Walter B. Martin, president of the American Medical Association, recently stated that he had tabulated the social and economic problems confronting the medical profession, and among them found 30 which he considered important. To these can be added those peculiar to various localities. The proper solutions can be reached only through a strong organization starting in the district societies, backed with adequate funds, and with the active support of many well-informed physicians.

SCIENTIFIC PROGRAM

Tuesday, May 3, 1955

Doctor Woutat: We now proceed to the recognition of our honorary and "50 Year Club" members. Will those men who are in the audience please come to the platform: Doctor P. G. Arzt, Doctor O. C. Gaebe, and Doctor A. M. Fisher; we are very happy to have you gentlemen here with us today. I think it is quite fitting that we should pause and pay some respects to these gentlemen. My father started practicing in North Dakota in 1899, so I know a little of the problems and difficulties of these older practitioners. I feel that, if time allowed, these men could tell us interesting tales of difficulties and of many remarkable accompilshments with techniques which seem to us today somewhat crude; just as our methods will appear crude 30 years hence.

We are very happy to have you here to give you a little token of our esteem. Fifty years is a long time. The honorary members have been licensed to practice medicine in North Dakota for 50 years, and the "50 Year Club" members have been licensed to practice medicine for 50 years.

Doctor Arzt, here is a little certificate in appreciation of your fifty years of practice. Doctor Arzt graduated from the University of Minnesota and was licensed to practice medicine in 1905. He has been in Jamestown, North Dakota. We also have this "50 Year Club" pin for you.

Doctor A. M. Fisher is both an honorary member and a "50 Year Club" member. He was made a "50 Year Club" member in 1954, having graduated from Northwestern University and received his license to practice medicine in 1904, and received his North Dakota license in 1905. He was formerly at Jamestown, North Dakota.

Doctor O. C. Gaebe of New Salem, North Dakota, graduated from the University of Southern California and was licensed in 1905. Here is your certificate and pin.

The following two doctors could not attend, but we will send the certificates and pins by mail. Doctor O. T. Benson, formerly of Glen Ullin, North Dakota, now resides at North Hollywood, California. He graduated from the University of Minnesota and was licensed in 1905. Doctor Roy Lynde of Ellendale, North Dakota, is still active and could not be here today. He is both a "50 Year Club" member and an honorary member. He graduated from the University of Minnesota and was licensed in North Dakota in 1905. Doctor Jacob Van Houten of Valley City, North Dakota, receives both a pin for being "50 Year Club" member and a certificate for honorary membership, having graduated from Northwestern University in 1905.

Gentlemen, it is a pleasure to meet you and have you with us. I wish you many healthy, happy years.

Dr. R. H. Waldschmidt: I say this with deep regret, that our president-elect, Dr. D. J. Halliday, is ill and can not appear, much as he would like to. At this particular session, he has asked Dr. Woutat to present his inaugural address.

Dr. Woutat: We have sent Dr. Halliday our proper regrets that he has not been able to be with us. He has wisely consented to follow his physician's advise. He starts out with a few remarks about me, for which I thank him.

INAUGURAL ADDRESS

D. J. Halliday, M.D.

Allow me, Dr. Woutat, on behalf of the state medical association, to thank you for your splendid service, as president of the association. You have given freely of your time to further the cause of medicine in our state.

It is with a great deal of temerity that I assume the responsibilities of this office. My predecessors have attained and upheld high standards which, I pledge you, I shall strive to maintain.

Robert Louis Stevenson's eulogy to the doctor contains these words:

"There are men, and classes of men, that stand above the common herd; the soldier, the sailor and the shepherd, not infrequently; the artist rarely, rarelier still the clergyman; the physician almost as a rule. He is the flower of our civilization, and when that stage of man is done with, and only remembered to be marvelled at in history, he will be thought to have shared as little as any in the defects of the period, and most notably exhibited the virtues of the race."

The physician has long been the advisor and consultant in matters of sickness and health and he has always held a respected place in the community. With this favored position the doctor must assume the responsibility of leadership. The ones who love and respect him, look to him for guidance. But is he so immersed in private practice that he is deaf to this call? First, he must be a good American, and secondly, a good practitioner.

A good citizen is, I think, one who obeys the laws, exercises his right to vote, participates actively in community affairs, and is willing to serve on the city council, or school board. In these ways he makes his contribution to the preservation of liberty, justice and freedom.

At this time in our history there seems to be a strong disposition amongst our citizenry to "let Uncle Sam do it." They live in a dream world of little effort and look forward to social seeurtiy and old age benefits in their "sere and yellow leaf." Let us train our young people not to tread this "primrose path of dalliance."

Medicine has progressed at a prodigious rate during the past fifty years. There have been more scientific advances in this period than in all the preceding centuries. For example, death rates from disease have declined to such a degree that the average longevity in the United States has increased since 1900 from 49.2 years to 66.7 years.

What has been the most important advance of all during this period of unprecedented progress? At first thought, one might be tempted to name a specific discovery which has revolutionized modern clinical practice: penicillin, insulin, or Salk vaccine. Dr. Barry Woods, Jr., professor of medicine in St. Louis, is convinced that the most important medical advance in the United States, since the turn of the century, has been none of these,

but rather a change in the attitude of the practicing physician toward medical science, brought about by the standardization of the medical schools. He says Dr. Flexner's criticisms of medical education in 1910 initiated an immediate revolution in medical education. They spelled the doom of the numerous proprietary diploma mills of medicine, then prevalent, and led to the establishment instead of university medical schools. All of the remarkable advances in the past fifty years would not now be a part of medical history if the intellectual climate of medical schools had remained unchanged.

We, who are practicing in this phenomenal era, must keep ourselves well informed in medical research by reading, postgraduate study and attendance at medical meetings, such as this. We have a service to perform to society; so let us discharge our obligations with our best efforts. As physicians, let us bear in mind the part we play in public relations.

Our association with our colleague, the patient, the public and the press should ever be friendly, helpful and constructive. May pity and compassion lend us their powerful wings. Let us adopt, as our watchword, Trudeau's meaningful lines:

"To cure — sometimes,
To relieve — often,
And to comfort — always."

Dr. Woutat: Dr. Halliday is now your president, and Dr. R. H. Waldschmidt your president-elect. I ask for Dr. Halliday the same wonderful cooperation you have extended to me.

North Dakota State Medical Association Roster-1955

MEMBERSHIP BY DISTRICTS

DEVILS LAKE

Corbett, C. A. — Lake Region Clinic, Devils Lake
Engesather, J. A. D. — Lakota
Fawcett, J. C. — Lake Region Clinic, Devils Lake
Fawcett, R. M. — Lake Region Clinic, Devils Lake
Fox, W. R. — Johnson Clinic, Rugby
Gilchrist, Milton R. — Rolla
Goodman, Edward H. — Rolla
Hilts, G. H. — Cando
Johnson, C. G. — Johnson Clinic, Rugby
Longmire, Thomas — 411 4th Ave., Devils Lake
Keller, E. T. — Johnson Clinic, Rugby
Lazareck, I. L. — 411 4th Ave., Devils Lake
MacDonald, J. A. — Cando
Mahoney, J. H. — 411 4th Ave., Devils Lake
Owens, C. G. — New Rockford
Palmer, D. W. — Cando
Pine, L. F. — Lake Region Clinic, Devils Lake
Schwinghamer, E. J. — New Rockford
Seibel, Glenn W. — New Rockford
Sihler, W. F. (honorary) — Mann Block, Devils Lake
Stickelberger, Josephine S. (honorary) — 1524 Portland Ave., St. Paul 5, Minn.
Terlecki, J. — Minnewaukan
Thordarson, J. D. — Maddock
Toomey, Glen W. — Lake Region Clinic, Devils Lake
Vigeland, G. N. — Johnson Clinic, Rugby
Voglewede, W. C. — Carrington

FIRST

Amidon, Blaine F. — 702 1st Ave. S., Dakota Clinic, Fargo
Armstrong, W. B. — 702 1st Ave. S., Dakota Clinic, Fargo
Bacheller, S. C. — Enderlin
Bakke, Hans — Lisbon
Barnard, Donald — 807 Broadway, Fargo Clinic, Fargo
Bateman, C. V. — 310 Dakota Ave., Wahpeton
Beithon, E. J. — 403 N. 7th St., Wahpeton
Beithon, Paul J. (in service) — Wahpeton
Beltz, Melvin E. — 207 6th St. N., Wahpeton
Borland, V. G. — 807 Broadway, Fargo Clinic, Fargo
Burt, A. C. — 405 Black Bldg., Fargo
Christoferson, Lee — 435 deLendrecie Bldg., Fargo
Clark, I. D., Jr. — Casselton
Corbus, B. C. — 304 Black Bldg., Fargo
Crim, Eleanor — 1701 13th St., Fargo
Darner, C. B. — 807 Broadway, Fargo Clinic, Fargo
Darrow, F. I. (retired) — 706 8th St. S., Fargo
Darrow, K. E. — 702 1st Ave. S., Dakota Clinic, Fargo
DeCesare, F. A. — 702 1st Ave. S., Dakota Clinic, Fargo
Dillard, J. R. — 314 Black Bldg., Fargo
Dodds, G. A. — 807 Broadway, Fargo Clinic, Fargo
Donat, T. L. — 702 1st Ave. S., Dakota Clinic, Fargo
Fortin, H. J. — 313 Black Bldg., Fargo
Fortney, A. C. — 807 Broadway, Fargo Clinic, Fargo
Foster, George C. — 507 1st Natl. Bank Bldg., Fargo
Geib, M. J. — 32 North 3rd, Moorhead, Minn.
Gillam, John S. — 807 Broadway, Fargo Clinic, Fargo
Gronvold, F. O. (honorary) — 910 Broadway, Fargo
Gustafson, Maynard B. — 435 deLendrecie Bldg., Fargo
Hall, G. H. — 807 Broadway, Fargo Clinic, Fargo
Haugrud, E. M. — 304 Black Bldg., Fargo
Hawn, H. W. — 807 Broadway, Fargo Clinic, Fargo
Heilman, C. O. — 807 Broadway, Fargo Clinic, Fargo
Hunter, C. M. — 311 Black Bldg., Fargo
Hunter, G. W. — 807 Broadway, Fargo Clinic, Fargo
Huntley, H. B. — Kindred
Irvine, V. S. — Lidgerwood
Ivers, G. U. — 424 deLendrecie Bldg., Fargo
Jaehning, David — 403 N. 7th St., Wahpeton
Kiesel, Ilmar — Page
Klein, A. L. — 55½ Broadway, Fargo
Koons, Wilbur — Lidgerwood
Kulland, Roy — 136 South 1st St., West Fargo
Lancaster, W. E. G. — 807 Broadway, Fargo Clinic, Fargo
Landa, Marshall — 702 1st Ave. S., Dakota Clinic, Fargo
Larson, G. A. — 608 Black Bldg., Fargo
Lawrence, Donald H. — 217½ Broadway, Fargo
LeBien, W. E. — 807 Broadway, Fargo Clinic, Fargo
LeMar, John — 807 Broadway, Fargo Clinic, Fargo
Lewis, A. K. — Lisbon
Lewis, T. H. — 302 Black Bldg., Fargo
Lindsay, D. T. — 807 Broadway, Fargo Clinic, Fargo
Long, W. H. — 702 1st Ave. S., Dakota Clinic, Fargo
Lytle, F. T. — 807 Broadway, Fargo Clinic, Fargo
Macaulay, W. L. — 807 Broadway, Fargo Clinic, Fargo
Mazur, B. A. — 702 1st Ave. S., Dakota Clinic, Fargo
Melton, Frank M. — 702 1st Ave. S., Dakota Clinic, Fargo
Miller, H. H. — 509½ Dakota Ave., Wahpeton
Morris, A. H. (honorary) — 608 Front, Fargo
Nagle, Duane W. — Enderlin

Nichols, W. C. 807 Broadway, Fargo Clinic, Fargo
Norum, Henry A. 807 Broadway, Fargo Clinic, Fargo
Nuessle, Wm. F. 702 1st Ave. S., Dakota Clinic, Fargo
Oftedal, Trygve 403 Black Bldg., Fargo
Poindexter, M. H. 807 Broadway, Fargo Clinic, Fargo
Pray, L. G. 807 Broadway, Fargo Clinic, Fargo
Rogers, Robert G. 702 1st Ave. S., Dakota Clinic, Fargo
Schleinitz, F. B. Hankinson
Schneider, J. F. 804 Black Bldg., Fargo
Sedlak, O. A. 702 1st Ave. S., Dakota Clinic, Fargo
Skjelset, A. G. 807 Broadway, Fargo Clinic, Fargo
Spier, Jack J. 388 6th Ave. S., Fargo
Stafne, W. A. 807 Broadway, Fargo Clinic, Fargo
Swanson, J. C. 407 Black Bldg., Fargo
Tronnes, Nels (honorary) 1119 Broadway, Fargo
Urenn, B. M. 702 1st Ave. S., Dakota Clinic, Fargo
Veitch, Abner Lisbon
Wall, Wendell Wahpeton Clinic, Wahpeton
Walter, Paul A. F. Lisbon
Wasemiller, E. R. Wahpeton Clinic, Wahpeton
Webster, William O. 807 Broadway, Fargo Clinic, Fargo
Weible, R. D. 702 1st Ave. S., Dakota Clinic, Fargo
Wiltse, Glenn L. Wahpeton Clinic, Wahpeton
Winge, Herbert C. 310 Dakota Ave., Wahpeton
Wold, Lester E. 807 Broadway, Fargo Clinic, Fargo
Zauner, Richard J. 311 Black Bldg., Fargo

GRAND FORKS

Adams, Paul V. Langdon
Benson, T. Q. 323½ DeMers Ave., Grand Forks
Benwell, H. D. 4½ S. 3rd, Grand Forks
Berger, Philip R. Grand Forks Clinic, Grand Forks
Boynton, Bruce Box 228, Grafton
Campbell, R. D. (honorary) 323 S. 6th St., Grand Forks
Cardy, J. D. University of North Dakota, Grand Forks
Chasten, Stephen M. 1101 Reeves Drive, Grand Forks
Connor, John F. Cavalier
Countryman, G. L. Grafton
Culmer, A. E., Jr. 501 1st Natl. Bank Bldg., Grand Forks
Dailey, Walter C. 4½ S. 3rd, Grand Forks
Deason, F. W. Box 348, Grafton
DeLano, Robert H. Northwood
Durkin, J. W., Jr. Grafton Natl. Bank Bldg., Grafton
Flaten, A. N. Edinburg
Fritzell, K. E. Grand Forks Clinic, Grand Forks
Froke, Leo B. Grand Forks Clinic, Grand Forks
Glaspel, C. J. Box 228, Grafton
Goehl, R. O. Grand Forks Clinic, Grand Forks
Graham, C. M. 11 N. 5th, Grand Forks
Graham, John 15½ S. 3rd, Grand Forks
Grinnell, E. L. Grand Forks Clinic, Grand Forks
Hardy, N. A. Minto
Harwood, T. H. Univ. of North Dakota, Grand Forks
Haugen, C. O. Larimore
Haunz, Edgar A. Grand Forks Clinic, Grand Forks
Hill, Frank A. Grand Forks Clinic, Grand Forks
Jensen, A. F. Grand Forks Clinic, Grand Forks
Johanson, John F. Cavalier
Kohlmeyer, A. C. Larimore
Lamont, J. G. (honorary) 1108 Woodlawn Drive, Brookhaven Addition, Oklahoma City, Oklahoma
Landry, L. H. Walhalla
Leigh, James A. 111 N. 5th, Grand Forks
Leigh, R. E. 111 N. 5th, Grand Forks
Lommen, C. E. Fordville
Mahowald, R. E. 504 Red River Natl. Bank Bldg., Grand Forks
Moore, J. H. Grand Forks Clinic, Grand Forks
Muus, J. Meyer McVille
Muus, O. H. 502 Red River Natl. Bank Bldg., Grand Forks
Nelson, Wallace W. Grand Forks Clinic, Grand Forks
Osten, Taylor A. Michigan
Painter, Robert C. Grand Forks Clinic, Grand Forks
Panek, A. F. Milton
Papenfuss, Harlan L. University of North Dakota, Grand Forks
Peake, F. Margaret 14½ S. 3rd, Grand Forks
Peterkin, Frank D. Langdon
Pettit, Samuel L. Grand Forks Clinic, Grand Forks
Piltingsrud, H. R. Park River
Porter, Charles B. Grand Forks Clinic, Grand Forks
Prochaska, L. J. 303 Security Bldg., Grand Forks
Quale, V. S. 407 1st Natl. Bank Bldg., Grand Forks
Ralston, Lloyd S. Grand Forks Clinic, Grand Forks
Rand, C. C. Grafton State School, Grafton
Revere, Jack W. Grand Forks Clinic, Grand Forks
Ruud, H. O. 414 First Natl. Bank Bldg., Grand Forks
Ruud, John E. 414 First Natl. Bank Bldg., Grand Forks
Sandmeyer, John A. Grand Forks Clinic, Grand Forks
Silverman, Louis B. Grand Forks Clinic, Grand Forks
St. Clair, Robert T. 517 First Natl. Bank Bldg., Grand Forks
Strom, Adrian D. Langdon
Talbert, M. J. 4½ S. 3rd St., Grand Forks
Teevens, W. P. Grafton Clinic, Grafton
Thorgrimson, G. G. 404 Security Bldg., Grand Forks
Tompkins, C. R. 641 Kittson Ave. S., Grafton
Tsumagari, Henry Y. (in service) Grand Forks
Turner, R. C. Grand Forks Clinic, Grand Forks
Waldren, H. M., Jr. Drayton
Witherstine, W. H. 111 N. 5th, Grand Forks
Woutat, P. H. Grand Forks Clinic, Grand Forks
Youngs, N. A. Grand Forks Clinic, Grand Forks

KOTANA

Blankstein, Frederic Watford City
Craven, J. D. 411 Main St., Williston
Craven, J. P. 411 Main St., Williston
Ellis, Gordon E. Harmon Park Clinic, Williston
Froeschle, Rudolph P. Hazen
Hagan, E. J. 411 Main St., Williston
Johnson, A. K. Williston Clinic, Williston
Johnson, P. O. C. Watford City
Korwin, J. J. 120 Main, Williston
Lamal, Andre H. Watford City
Lund, C. M. Williston Clinic, Williston
McPhail, C. O. Crosby
Pile, Duane F. Crosby
Sathe, Andrew G. Harmon Park Clinic, Williston
Skjei, D. E. Williston Clinic, Williston
Strinden, Dean R. Harmon Park Clinic, Williston
Wright, W. A. Williston Clinic, Williston

NORTHWEST

Amstutz, K. N. Northwest Clinic, Minot
Anderson, Gordon D. Harvey
Ayash, John J. 119A Main St., Minot
Blatherwick, Robert Parshall
Blatherwick, W. E. New Town
Boyum, Lowell E. Harvey
Boyum, P. A. Harvey
Breslich, Paul J. Northwest Clinic, Minot
Cameron, A. L. Northwest Clinic, Minot
Clark, Joseph H. Northwest Clinic, Minot
Conroy, M. P. 214 Main St. S., Minot
Craise, O. S. Towner
Cranston, Robert (taking residency) Tioga
Devine, J. L., Jr. 17A Central Ave. W., Minot

Devine, J. L., Sr. (honorary)	17A Central Ave. W. Minot
Dormont, R. E.	Northwest Clinic, Minot
Erenfeld, F. R.	617 2nd Ave. N.W., Minot
Fischer, V. J.	105 Central Ave. E., Minot
Flath, M. G.	Stanley
Gammell, R. T.	Kenmare
Garrison, M. W.	Garrison Bldg., Minot
Giltner, Lloyd A.	105 E. Central Ave., Minot
Girard, Bernard A.	Mohall Clinic, Mohall
Goodman, Robert	Powers Lake
Greene, E. E.	Westhope
Halliday, D. J.	Kenmare
Halverson, C. H.	1st National Bank Bldg., Minot
Hammargren, A. F.	Harvey
Hart, George M.	Northwest Clinic, Minot
Hochhauser, Martin	Garrison
Hoopes, Lorman L.	17A S. Main St., Minot
Hordinsky, B. Z.	Drake
Horner, David B.	Northwest Clinic, Minot
Huntley, Wellington B.	17 Central Ave. W., Minot
Hurly, Wm. C.	Garrison Bldg., Minot
Johnson, J. A. (honorary)	Bottineau
Johnson, O. W.	Johnson Clinic, Rugby
Johnson, Robert O.	Bottineau
Kermott, L. H., Jr.	12A S. Main, Minot
Kermott, L. H., Sr.	12A S. Main, Minot
Kitto, William	Northwest Clinic, Minot
Knudson, K. O.	431 7th St. N.W., Minot
Lampert, M. T.	407 1st Natl. Bank Bldg., Minot
Larson, R. S.	Velva
Loeb, George L.	State Hospital, San Haven
London, Carl B.	Northwest Clinic, Minot
McArdle, John S.	17A Central Ave. W., Minot
McCannel, A. D.	505 Main St. S., Minot
Malvey, Kenneth	Bottineau
Naegeli, F. D.	Northwest Clinic, Minot
Nelson, L. F.	Bottineau
Olson, B. G.	McCannel Clinic, Minot
Richardson, Gale R.	12 S.W. 10th St., Minot
Rowe, P. H.	Northwest Clinic, Minot
Schnee, Charles	Harvey
Seiffert, G. S.	Northwest Clinic, Minot
Shea, Samuel	McCannel Clinic, Minot
Sorenson, A. R.	105 E. Central Ave., Minot
Sorenson, Rodger	105 E. Central Ave., Minot
Taylor, William R. (in service)	Kenmare
Uthus, O. S.	21½ 2nd Ave. S.E., Minot
Veenbass, Fred F.	Northwest Clinic, Minot
Wall, W. W.	Northwest Clinic, Minot
Wallis, Marianne	St. Joseph's Hospital, Minot
Wheelon, F. E. (honorary)	609 9th Ave. S.E., Minot

SHEYENNE VALLEY

Christianson, Gunder	117 N.W. 3rd, Valley City
Fennell, William L.	Cooperstown
Gilsdorf, W. H.	117 N.W. Third, Valley City
Klein, C. J.	117 N.W. 3rd, Valley City
Macdonald, A. C.	130 Central Ave. S., Valley City
Macdonald, Niel A.	130 Central Ave. S., Valley City
Merrett, J. P.	117 N.W. 3rd, Valley City
Van Houten, J. (honorary)	105 Main St. W., Valley City
Wakefield, Kenneth	Cooperstown
Wicks, Edwin O.	133 N.W. 3rd St., Valley City
Wicks, F. L.	726 Chautauqua Blvd., Valley City

SIXTH

Arneson, C. A.	Missouri Valley Clinic, Bismarck
Baumgartner, C. J.	Quain & Ramstad Clinic, Bismarck
Benson, O. T.	1737 Whitley Ave., Hollywood, Calif.
Berg, H. M.	Quain & Ramstad Clinic, Bismarck
Berthea, H. J.	Linton
Blumenthal, Philip	107 1st Ave. N.W., Mandan
Bodenstab, W. H. (honorary)	520 Mandan St., Bismarck
Boerth, E. H.	Quain & Ramstad Clinic, Bismarck
Boyle, John T.	Garrison
Brink, N. O.	Quain & Ramstad Clinic, Bismarck
Buckingham, T. W.	405½ Broadway, Bismarck
Cartwright, John	Missouri Valley Clinic, Bismarck
Dahl, Philip	Missouri Valley Clinic, Bismarck
Davidson, Hugh R.	Riverdale
De Moully, O. M.	Flasher
Diven, W. L.	402½ Main Ave., Bismarck
Enders, W. R.	Hazen
Ericksen, Johan A.	Quain & Ramstad Clinic, Bismarck
Fisher, A. M. (honorary)	General Delivery, Bismarck
Fredricks, L. H.	Quain & Ramstad Clinic, Bismarck
Freise, P. W.	Quain & Ramstad Clinic, Bismarck
Gaebe, O. C.	New Salem
Goughnour, Myron	405½ Broadway, Bismarck
Gregware, P. Roy	Quain & Ramstad Clinic, Bismarck
Griebenow, F. F.	905 9th St., Bismarck
Gutowski, Franz	Wishek
Harrington, James F.	107 1st Ave. N.W., Mandan
Heffron, M. M.	412½ Main, Bismarck
Henderson, R. W.	405½ Broadway, Bismarck
Hetzler, A. E.	322 Main W., Mandan
Icenogle, G. D.	Quain & Ramstad Clinic, Bismarck
Jacobson, M. S.	Elgin
Johnson, Kenneth J.	Quain & Ramstad Clinic, Bismarck
Johnson, Marlin J. E.	Quain & Ramstad Clinic, Bismarck
Johnson, Paul L.	Quain & Ramstad Clinic, Bismarck
Kalnins, Arnold	Washburn
Kling, Robert R.	Quain & Ramstad Clinic, Bismarck
Kuplis, Haralds	Turtle Lake
LaRose, V. J. (honorary)	712 Mandan St., Bismarck
Larson, L. W.	Quain & Ramstad Clinic, Bismarck
Levi, W. E.	Beulah
Lipp, G. R.	405 Broadway, Bismarck
Marr, Valentine C.	Glen Ullin
Mears, Edward J.	Quain & Ramstad Clinic, Bismarck
Nuessle, R. F.	Quain & Ramstad Clinic, Bismarck
Nugent, M. E.	Quain & Ramstad Clinic, Bismarck
Oja, Karl	Ashley
Orr, A. C.	405½ Broadway, Bismarck
Owens, P. L.	Missouri Valley Clinic, Bismarck
Perrin, Edwin D.	Quain & Ramstad Clinic, Bismarck
Peters, Clifford	Quain & Ramstad Clinic, Bismarck
Pierce, W. B.	Quain & Ramstad Clinic, Bismarck
Quain, E. P. (honorary)	2075 Raynor St., Salem, Ore.
Radl, R. B.	Quain & Ramstad Clinic, Bismarck
Saxvik, R. O.	State Hospital, Jamestown
Schoregge, C. W.	Quain & Ramstad Clinic, Bismarck
Schoregge, R. D.	Quain & Ramstad Clinic, Bismarck
Smith, C. C.	506 N.W. 3rd, Mandan
Smith, Clyde L.	Missouri Valley Clinic, Bismarck
Spielman, George (retired)	305 1st Ave. N.W., Mandan
Thompson, Arnold	Quain & Ramstad Clinic, Bismarck
Tudor, Robert B.	Quain & Ramstad Clinic, Bismarck
Vinje, E. G.	Hazen
Vinje, Ralph	206 9th St., Bismarck
Vonnegut, F. F.	Linton
Waldschmidt, R. H.	Quain & Ramstad Clinic, Bismarck
Walter, Eric	Quain & Ramstad Clinic, Bismarck
Weyrens, P. J.	Hebron
Wittchow, Allen W.	Quain & Ramstad Clinic, Bismarck
Zukowski, Anthony	Steele

SOUTHWESTERN

Buckingham, William M.	Elgin
Bush, Clarence A.	Beach
Curiskis, Adolf	New England
Dukart, C. R.	Dickinson Clinic, Dickinson
Dukart, Ralph	Dickinson Clinic, Dickinson
Foster, Keith G.	109 7th St. W., Dickinson
Gilliland, R. F.	Dickinson Clinic, Dickinson
Gilsdorf, A. R.	Dickinson Clinic, Dickinson
Guloien, H. E.	Dickinson Clinic, Dickinson
Goulding, Robert L.	Bowman
Gumper, A. J.	109 7th St. W., Dickinson
Hankins, Robert E.	Mott
Hills, S. W.	Regent
Hilts, Joseph A.	Hettinger
Larsen, Harlan C.	109 7th St. W., Dickinson
Maercklein, O. C. (retired)	Mott
Martens, Apollon	Bowman
Martin, Gladys	Dickinson Clinic, Dickinson
Moses, James	Richardton
Murray, K. M. (retired)	Scranton
Reichert, D. J.	Reichert Bldg., Dickinson
Reichert, H. L.	Reichert Bldg., Dickinson
Rodgers, R. W.	109 W. 7th St., Dickinson
Schumacher, Wm. A.	Hettinger
Smith, Oscar M. (retired)	509 1st Ave. W., Dickinson
Spear, A. E. (retired)	610 1st Ave. W., Dickinson
Tosky, Julien	Hebron

STUTSMAN

Arzt, P. G.	DePuy-Sorkness Clinic, Jamestown
Beall, John A.	Medical Arts Clinic, Jamestown
Crayehee, W. A.	Oakes
Elsworth, J. N.	DePuy-Sorkness Clinic, Jamestown
Fandrich, Harry	Medina
Fergusson, V. D.	Edgeley
Freeman, John G.	State Hospital, Jamestown
Gronewald, Tula W.	State Hospital, Jamestown
Hayward, Mark	Gackle
Hieb, Edwin O. (taking residency)	Jamestown
Hogan, C. W.	DePuy-Sorkness Clinic, Jamestown
Holt, G. H.	102½ 1st Ave. S., Jamestown
Jansonins, J. W.	Medical Arts Clinic, Jamestown
Kooiker, Robert H.	State Hospital, Jamestown
Kristjansson, Gestur	Ellendale
Kuisk, Hans	Rutland
Larson, E. J.	DePuy-Sorkness Clinic, Jamestown
Lucy, R. E.	DePuy-Sorkness Clinic, Jamestown
Lynde, Roy (honorary)	Ellendale
McFadden, Robert L.	DePuy-Sorkness Clinic, Jamestown
Martin, Clarence S.	Kensal
Melzer, S. W. (retired)	Woodworth
Miller, Samuel	DePuy-Sorkness Clinic, Jamestown
Nierling, R. D.	DePuy-Sorkness Clinic, Jamestown
Oster, Ellis	Ellendale
Pederson, T. E.	DePuy-Sorkness Clinic, Jamestown
Sorkness, Joseph	DePuy-Sorkness Clinic, Jamestown
Steidl, Richard M.	Mohall
Turner, Neville W.	LaMoure
Van Der Linde, J. M.	Medical Arts Clinic, Jamestown
Van Houten, R. W.	Oakes
Woodward, Robert S.	DePuy-Sorkness Clinic, Jamestown
Young, John	State Hospital, Jamestown

TRAILL-STEELE

Kjelland, A. A.	Hatton
Knutson, O. A. (honorary)	Buxton
LaFleur, H. A.	Mayville
Little, R. C.	Mayville
McLean, Robert W.	Hillsboro
Mergens, Daniel N.	Hillsboro
Pearson, L. O.	Mayville
Vandergon, Keith G.	Portland
Vinje, Syver	Hillsboro
Waydeman, H. Burrell	Hunter

NINTH ANNUAL MEETING
WOMAN'S AUXILIARY TO THE NORTH DAKOTA STATE MEDICAL ASSOCIATION
Bismarck, North Dakota, April 30, May 1, 2, and 3, 1955

The ninth annual meeting of the Woman's Auxiliary to the North Dakota State Medical Association was held in the Bismarck Municipal Country Club, Monday, May 2, 10:00 a.m. The meeting was formally opened by Mrs. S. C. Bacheller, president.

The pledge of loyalty was given by Mrs. J. H. Mahoney, and repeated in unison by the members present. The group stood together for a silent prayer for peace.

Mrs. M. M. Heffron, Bismarck, gave the address of welcome on behalf of the Woman's Auxiliary of the Sixth District. She introduced Mrs. C. A.. Arneson, convention chairman, and Mrs. R. F. Nuessle.

Mrs. E. T. Keller gave the response.

Greetings were then given by Dr. R. F. Nuessle, president, Sixth District Medical Society.

Mrs. S. C. Bacheller, president, then introduced our honored guest and speaker, Mrs. Harlan English, Danville, Illinois, national second vice-president of the Woman's Auxiliary to the American Medical Association.

The roll was called by the recording secretary, Mrs. J. W. Jansonius, and the following were present: Mrs. S. C. Bacheller, president; Mrs. J. H. Mahoney, president-elect; Mrs. C. A. Arneson first vice-president; Mrs. J. W. Jansonius, recording secretary; and Mrs. V. J. Fischer, treasurer.

State chairmen: Mrs. H. L. Kermott, nominating and bulletin; Mrs. Clyde L. Smith, legislation; and Mrs. G. D. Gertson, rural health.

District presidents: Mrs. L. E. Wold, Fargo; Mrs. J. D. Cardy, Grand Forks; and Mrs. R. L. McFadden, Jamestown.

Delegates: Mrs. O. A. Sedlak, Fargo; Mrs. Frank De Cesare, Fargo; Mrs. Hugh Hawn, Fargo; Mrs. R. O. Goehl, Grand Forks; Mrs. W. B. Huntley, Minot; Mrs. Marlon Johnson, Bismarck; Mrs. R. D. Nierling, Jamestown; and Mrs. Robert Gilliland, Dickinson.

Councillors: Mrs. O. M. De Moully, Flasher.

Student loan fund committee: Mrs. Carl Baumgartner, Bismarck.

Mrs. H. M. Berg, Mrs. Clyde Smith, and Mrs. C. A. Arneson were appointed to serve on the reading committee for the minutes of the convention.

Mrs. V. J. Fischer then read the following treasurer's report:

Financial Statement—1954-1955

Receipts:		
Balance on hand, July 1954	$ 894.37	
Dues:		
294 members at $4.00	1,176.00	
1 honorary member		
1 arrears at $3.00	3.00	
296 members		
Sale of handbooks	2.45	
Sophomore student loan fund contributions	2,339.96	
State medical association, convention fund contribution	200.00	
Registration fee at convention, Bismarck	85.00	
4 "Bulletin" subscriptions included in dues check from Devils Lake	4.00	
Total receipts		$4,704.78
Disbursements:		
Dues to national	$ 296.00	
University of North Dakota sophomore student loan fund	2,339.96	
President's expenses:		
National A.M.A. convention, San Francisco	$ 284.66	
Chicago conference	88.27	
Miscellaneous	36.74	
President-elect's expenses:		
Chicago conference	79.56	
Miscellaneous	5.00	
Stationery	30.86	
President's corsage for A.M.A.; Mrs. S. C. Bacheller	8.65	
President's corsage, Mrs. J. H. Mahoney	5.00	
News Letter, 2 issues	57.22	
Standing Committees:		
News Letter	5.50	
Student loan fund	13.51	
"Bulletin"	2.00	
Treasurer	7.85	
President's pin	7.34	
Four Bulletin subscriptions included in Devils Lake dues check. Paid to Bulletin chairman	4.00	
Gift for Mrs. Mason G. Lawson, Little Rock, Ark.; national president and North Dakota honorary member	11.00	
Convention expenses, Bismarck	214.63	
	$3,497.75	
Balance on hand, June 30, 1955		$1,207.03

The following reports were given by the officers, state chairman, and auxiliary presidents:

President's Report

It is with mixed emotions that I submit my final report as president of the auxiliary to the North Dakota State Medical Association. It will be a relief to turn my responsibilities over to the exceedingly able incoming president. However, I also do this with regret, since I have enjoyed the contacts and honors that have been bestowed on me as your president.

Our theme for the year has been "Know Your Auxiliary." This was chosen with the thought that if we, as members, had a better understanding of the tremendous potential of the auxiliary, we could make it a better and stronger organization.

Our successes and failures for the year have also been mixed.

Our very young medical student loan fund has been increased by $2,339.96, to make a total of $6,700.28 raised since its origin in 1950.

Membership in the 10 districts has been increased by 28 members, to make a total of 295.

Today's Health has not increased in proportion to last year's gain. We have 146 credits and are proud to have one "exclusive district" with 183 per cent of their quota.

The AMEF committee was established for the first time this year with contributions totaling $41. It is hoped that as the various districts become more familiar with this fund we can make a sizeable contribution.

In nurse recruitment, various districts have assisted in local projects. Our new future nurses club was sponsored. A number of nurse recruitment films have been shown to interested groups. At present, an attempt is being made to determine how many nurse loan funds and nurses scholarships are available in the state. This list will be sent to each of our high schools.

Public relations have been improved through the work of individual members who have devoted time to filter centers, immunization clinics, the National Foundation for Infantile Paralysis, Easter seals, hospital auxiliaries, girl scouts, cub scouts, Christmas baskets for the needy, opportunity school, Red Cross, and other community projects too numerous to mention.

WDAY-TV and KXJB-TV cooperated with us in showing two AMA public service films, "Operation Herbert," and "A Life to Save."

Mental health programs have had the support of many auxiliaries, and we have members on local and state mental health boards.

Three interesting and informative News Letters were published this year.

Legislation has been of great interest to us this year. We successfully supported a bill providing special funds for exceptional children and a bill giving state scholarships for nurses. We successfully opposed an anti-fluoridation bill and an osteopathic bill.

Programs have been planned to: (1) interest members in the aims and objectives of the auxiliary; (2) to provide authentic information concerning health standards and auxiliary health projects; and (3) to generate a "warmth of fellowship" among physicians' families.

The majority of the districts have 4 to 5 meetings per year, and usually hold their meetings at the same time that their physician-husbands meet for their regular district medical meetings. The auxiliary meetings usually are a dinner meeting with business session, a prepared program, social hour, or both.

The resolutions chairman has adopted a new simplified type of resolution which we consider an improvement over the older style.

The rural health chairman has cooperated with state rural health committees.

The *Bulletin* subscriptions have increased and one district has 100 per cent subscribing.

The state historian has kept her records up to date and has purchased a new scrap book with the name of our society printed on the cover.

It has been my pleasure to attend meetings in 6 districts, the state convention, two state board meetings, the national convention, and the national conference meeting in Chicago, as well as a press and publicity meeting sponsored by the North Dakota State Medical Association. It was also my privilege to be asked to speak before the house of delegates of the North Dakota Medical Association at their annual meeting which is held during the state convention at Bismarck.

The main topic for my talks, when visiting the districts, has been the importance of self-education. If we, as doctor's wives, can give information rather than misinformation to our lay contacts, it can bring about better understanding between the medical profession and the public.

In an attempt to overcome the inconvenience of having 295 members scattered over 70,665 square miles I have written 200 letters and innumerable cards in connection with auxiliary activities.

My post-term project will be to write a president's handbook for the North Dakota Auxiliary. This is to be in loose-leaf form and when it has been tested, revised, and approved, it can be printed in a permanent form.

In conclusion, I wish to thank the officers and committee chairmen of the North Dakota Auxiliary for their fine support and cooperation, the national officers and committee chairman for their support and guidance, and the central office staff for their assistance.

Mrs. Stephen C. Bacheller, President

Organization Report

This year we have increased our membership from 261 to 295, a gain of 34 members over last year, which we feel is very good. We are especially proud of sixth district, which raised its membership from 37 to 53, with 19 new members; and also Grand Forks district, which has 61 members, 100 per cent of the eligible members belonging. Other districts are as follows: First, 60; Devils Lake, 17; Kotana, 16; Northwest, 26; Sheyenne Valley, 10; Southwestern, 21; Stutsman, 23; Traill-Steele, 7; and our 1 honorary member, Mrs. Mason G. Lawson, who is now president-elect of the national auxiliary.

My thanks go to all the organization chairmen, and district presidents whose hard work and sincere efforts have effectively combined to produce this good record. It proves that patience and persistence eventually pay off productively toward an ever-increasing membership. So long as we continue to grow, we progress.

Mrs. James H. Mahoney,
Organization Chairman

Public Relations Report, 1954-1955

Six of the 10 auxiliaries filled out and returned the questionnaires sent them for their report. Again this year, the student loan fund raising campaign was the major project for all groups. However, the *Today's Health* program was of almost equal importance in some auxiliaries, one district obtaining 40 new subscriptions.

Future nurses' clubs were organized with much success, and nurse recruitment was carried out in cooperation with district nurses associations and schools.

The wide variety of projects to make for better public relations were numerous. Among these were active participation in civil defense, showing recommended films, and placing *Today's Health* in schools and libraries. Many groups worked in cooperation with district nurses associations, Red Cross, League of Women's Voters, county public health association, cancer societies, community councils, and the March of Dimes. The public was made aware of our activities by a bridge benefit and style show, teas of various kinds, and other social functions.

One district demonstrated wonderful public relations by donating $50 to a local opportunity school for handicapped children.

Although none of the auxiliaries sponsored a formal public relations program, as such, they have demonstrated their ability to make better public relations by active participation in a wide variety of projects. I hope the auxiliaries will continue their excellent work in public relations and in the future we will be able to report a complete organized effort from each district.

Mrs. J. D. LeMar, Chairman

Legislative Report, 1954-1955

As a comparative newcomer to North Dakota, I was grateful for the opportunity to serve as state legislation chairman. I found the experience both fascinating and educational.

Our national legislation chairman, Mrs. C. L. Goodhand, urged strongly that we make ourselves heard on matters of legislation important to the medical profession. To facilitate this action, I sent small sample information sheets to each district with the names of our national representatives, and I requested the legislation chairman or president of each district to fill in the names of her local state representatives. Also included was the proper method of addressing a letter to our representatives and a brief word on the type of letter which is most effective. Each local chairman was requested to see that every member in her district was provided with this information.

At the state legislative session, the medical profession was ably represented by Mr. Lyle Limond, executive secretary of the NDSMA. He has also kindly provided me with information on bills in which we were interested.

During the session 8 house and 7 Senate bills were of some concern to the medical profession. Listed here are a few of the varied types of bills: SB 18: Special education for exceptional children. NDSMA supported the bill. Governor has signed it; SB 117: Anti-fluoridation. We opposed this bill. It was defeated; HB 661: Nurse preparation scholarships. We were interested. Governor signed it; HB 834: The osteopath bill. (Would have given full drug and surgical privileges with instruments to the osteopaths.) We opposed this bill. It was defeated.

I quote Mr. Limond's remarks at the conclusion of his report on bills: "It is sincerely felt that medicine was not seriously harmed or set back appreciably in its program of providing every improving health care to all the people of North Dakota by the past legislative session."

The activities of the eighty-fourth Congress are well covered by the committee on legislation of the A.M.A. In the March 28, 1955, report from the A.M.A. Washington office, the position of the board of trustees of the A.M.A. on national health programs is given. Space limits prevent mention of all the bills; however, following are some of the highlights:

H.R. 3458, H.R. 3720: Title I—Federal health service reinsurance. Active opposition. Title VI—Grants to states for mental health programs. Active approval.

S. 781, H.R. 2096: To establish a U. S. Armed Forces medical academy. Active opposition.

H.R. 719: Construction of 16,000 additional VA hospital beds. Active opposition.

H.R. 9, H.R. 10: Tax postponement for self-employed. Active approval.

H.R. 445: Social security coverage extended to certain self-employed persons, including physicians. No opposition to voluntary coverage. Active opposition to compulsory coverage.

S.J. Res. 1: Proposed constitutional amendment relative to limiting the domestic effect of treaties and international agreements. Actively approved in principle because the bills would provide protection against the type of "backdoor" medical legislation now possible.

Become interested in legislation. You will find it worthwhile to be well informed, and your legislator will appreciate learning your opinion.

Mrs. Clyde L. Smith, Chairman

Program Report

Each year there has been an increased interest in the Woman's Medical Auxiliary by physicians' wives of North Dakota, with a steady growth of membership in the 10 district auxiliaries. This increased growth and interest is largely due to the aims and purposes of the program committee; namely (1) to interest members in the aims and objectives of the auxiliary and of the American Medical Association; (2) to provide authentic information concerning health standards and auxiliary health projects; and (3) to generate a "warmth of fellowship" among physicians' families.

The majority of the district auxiliaries have 4 to 5 meetings per year, and usually hold their meetings at the same time that their physician husbands meet for their regular district medical meetings. The auxiliary meetings usually are a dinner meeting with a business session, a prepared program, social hour, or both. Detailed accounts of programs and activities will not be given in this report because they are usually covered in each district auxiliary president's report. Only a few general projects and programs will be mentioned.

The medical student loan fund continues to be one of the main projects in the program of the North Dakota Woman's Medical Auxiliary. From money received through style shows, teas, contests, and similar activities, once again the physicians' wives will be able to turn over a substantial sum to further assist worthy medical students of the University of North Dakota medical school. Nurse recruitment, legislation, and mental health programs have been some of the other outstanding programs of our district auxiliaries.

The national program of the Woman's Medical Auxiliary for the 1954-1955 season has adopted the slogan, "Leadership in Community Health," and has stressed the following 12 items in its program: (1) greater familiarity with various functions, departments and services of the American Medical Association; (2) a family physician for every physician's family; (3) community health audits; (4) safety programs; (5) improvement of maternal and child care; (6) combating juvenile delinqueney; (7) promotion of mental hygiene; (8) study of the problems of ageing; (9) the need for nurse recruitment; (10) study of nutrition with special reference to overweight; (11) active participation in civil defense; and (12) support of legislation favorable to the freedom and dignity of the medical profession. It may be said that in some way or other the physicians' wives of North Dakota in their programs have, in their auxiliaries, taken part in almost every one of these 12 activities listed.

One project or program that should appeal to each physician's wife is to see that the physician's family has a family physician. Just as "the cobbler's children have no shoes," similarly the physician's family sometimes goes begging for medical attention. There is no one better situated than the physician's wife to be certain that her family, including her physician husband and herself, are provided with medical care. This example, and program right in our own homes should continue to occupy our utmost attention.

Many organizations have taken over style shows, benefit teas, etc., for the purpose of raising money. Because of this, the Woman's Medical Auxiliary should look to other means for raising money when necessary. One possibility that has great promise, and one that should be worth while, and at the same time, one that the Woman's Medical Auxiliary would have almost exclusive rights in its promotion, would be a health education program. This project could be an annual event with educational and ethical displays on health. The details of such a program cannot be outlined in this report; however, it would not entail a great deal of work. This activity could be held in some civic building with various booths and exhibits. Examples of various types of booths and organizations taking part in these displays are: first aid, Red Cross, crippled children, speech clinic, mental health, sight conservation, American Cancer Society, polio foundation, rural health, nurse recruitment, tuberculosis association, etc. With representative displays and booths of this nature, presented in an ethical manner for health education for laypeople, and with the backing of the local medical society, considerable favorable praise would be forthcoming to our Woman's Medical Auxiliary.

It is hoped that eventually every physician's wife in North Dakota will wish to play some part in the laudable programs of the Woman's Medical Auxiliary.

Mrs. Charles A. Arneson, Program Chairman

Nurse Recruitment Report

One district organized a second "future nurses" club. Another district attempted to organize one and was discouraged by the high school authorities.

Due to the fact that I started too late in the year to

prepare a list of nurse loans and scholarships, the list is not complete. Two districts sent very detailed reports, and a third district could report that there were no loans or scholarships. If any of the other 7 districts have information on this, it can perhaps be turned over to the new chairman.

The 1955 legislature passed a bill (House Bill 661) to aid the nurse shortage by giving nurse preparation scholarships.

MADA LEWIS, Chairman

Press and Publicity, 1954-1955

Due to my absence during December and January, only three *News Letters* were published this year. These 3 letters were rather lengthy to make up for the extra one.

The response from all the districts to my request for news has been excellent.

Along with the social news items and district activities, articles on current affairs in the medical world of interest to the members have been published.

MRS. G. G. THORGRIMSEN, Chairman

Rural Health Report

The Woman's Auxiliary to the North Dakota State Medical Association was invited to assist the national council on rural health at the sixth annual state medical convention in 1952.

Mrs. Henry Kermott was appointed the first rural health state chairman, and Mrs. G. D. Gertson was appointed in 1954 by Mrs. S. C. Bacheller, state president. Mrs. A. C. Kohlmeyer, chairman of rural health for the Grand Forks District Medical Auxiliary, has served on the state committee with Mrs. Gertson.

The North Dakota State Public Health Service and the North Dakota State Rural Health Council did not join in conference this year.

No request for assistance or rural health literature has been received.

MRS. G. D. GERTSON, Chairman

Historian's Report

Our state history is up to date and the *News Letters* have all been filed. Our historian bought a new history book with the name of our society engraved thereon in gold lettering.

MRS. D. J. HALLIDAY, Chairman

Bulletin Report

As of April 1, 1955, North Dakota had 55 subscriptions to the *Bulletin*, the official publication of the Woman's Auxiliary to the American Medical Association.

The Northwest District included subscriptions to the *Bulletin* and *Today's Health* with their dues. This practice was suggested by the national *Bulletin* chairman and might be considered in the future by all the districts in North Dakota.

MRS. HENRY KERMOTT, Chairman

"Today's Health" Report

The report of sales of *Today's Health* magazine for the year 1954-1955 is as follows:

District	*Quota*	*Credits*	*Percentage*
Northwest District	30	29	97%
Sixth District	37	17	46%
Grand Forks District	58	2	3%
Fargo District	55	44	80%
Stutsman District	21	22	105%
Traill-Steele	—	—	—
Sheyenne Valley District	10	4	40%
Kotana District	11	5	45%
Southwestern District	19	1	5%
Devils Lake District	12	22	183%
State totals and percentage	253	146	58%

MRS. J. A. BEALL, Chairman

American Medical Education Foundation Report

This is the first year there has been a chairman for this project. Memorial cards and material were distributed to all districts and an article written for the *News Letter*.

To date we have received 4 memorials totalling $41, and hope next year wil bring in many more.

Two were from the Devils Lake District for $10 each in memory of Dr. G. F. McIntosh and Dr. W. C. Follett. The third was from the First District; Ann R. Peterson, in memory of her niece, Dr. Irene Owens.

The fourth was from Mrs. John Cartwright, Mrs. Clyde Smith, and Mrs. M. M. Heffron, Sixth District, Bismarck, in memory of Dr. Irene Owens; and to be used for the University of Minnesota medical school.

MRS. W. E. G. LANCASTER, Chairman

State Student Medical Loan Fund Report

Needless to say, we are very proud and pleased to announce the year's intake from the state student loan fund. Many of you have doubled and some more than doubled your last year's donation. I congratulate all of you. Last year's amount: $1,405. This year's amount: $2,339.96.

District	*Membership*	*1954*	*1955*
Cass	60	$ 175.00	$ 270.00
Second (Devils Lake)	17	66.00	135.25
Grand Forks	61	363.00	751.71
Williston	15	55.00	55.00
Jamestown (Stutsman)	23	75.00	115.00
Sheyenne Valley	10	15.00	15.00
Southwest (Dickinson)	21	32.00	63.00
Sixth (Bismarck)	53	400.00	725.00
Minot	26	195.00	200.00
Traill-Steele	7	29.00	10.00
	Totals	$1,405.00	$2,339.96

Copy of report received from Mr. Olson, of the University business office, dated June 10, 1954.

Receipts:

7-2-51	Woman's Auxiliary	$1,047.76
8-25-52	Woman's Auxiliary	1,225.67
7-7-53	Woman's Auxiliary	1,121.85
3-1-54	Southwest Medical Auxiliary	32.00
5- -54	Woman's Auxiliary	1,373.00
		$4,800.28
Interest received on notes		8.74
	Total	$4,809.02

Notes outstanding:

1. Dated	7-2-51	$418.74
2. "	12-7-51	500.00
3. "	12-26-52	400.00
4. "	1-12-53	400.00
5. "	2-10-53	400.00
6. "	8-11-53	500.00
7. "	8-22-53	500.00
		$3,118.74
Balance in fund (just received)		$1,690.28

As against that amount, there is now pending another $500 loan.

MRS. CARL BAUMGARTNER, Chairman

Mental Health Report

Mental illness is a major problem in North Dakota. We have 2 institutions to care for the mentally ill: the State Mental Hospital at Jamestown and the State School for the Mentally Retarded at Grafton. About 2,018 patients are presently hospitalized at the State Hospital at Jamestown, and 1,179 persons are at the State School at Grafton. One for each 190 of our state's population is either at the Grafton School or the Jamestown Hospital. It is estimated that there are an additional 1,000 persons in North Dakota who should be added to the rolls of the State Hospital or other institutions and

agencies, under psychiatric management. North Dakota's institutions are grossly inadequate in terms of facilities and personnel. The patient load at the Jamestown Hospital is 500 greater than the institution's rated capacity. Although great progress has been made in the past year in obtaining professional personnel, the situation is far from adequate. The American Psychiatric Association recommends the following staff as compared to the present:

	Present	*Recommended*
Medical doctors	12	24
Registered nurses	12	133
Occupational therapists	5	8
Social service workers	2	12
Psychologists	7	5

The state school at Grafton is understaffed, and the facilities are inadequate to meet the needs of the institution's present enrollment. There is a long waiting list for applicants to Grafton. There is great need for a new school which should be located toward the western part of the state. At the present time, the Grafton School has no social service staff and has just recently been able to secure a psychologist. Much has been improved at the Grafton School recently and the future looks brighter, but in the case of both institutions, money and cooperation are needed. Before money and cooperation can fully be realized, the public is going to have to be educated. The general public, as well as the profession, do not react with the sympathy and understanding to the mentally ill as they do toward persons with bodily ills. The inadequate facilities and the shortage of personnel is a direct result of public neglect. We, in North Dakota, have not realized the problem that is facing us now.

Those who are trying to find a solution are hampered by a public attitude of disinterest or ignorance as to the problem of the mentally handicapped.

Mrs. G. G. Thorgrimsen, Chairman

Motion was made by Mrs. C. A. Arneson that we accept the reports of the state committee. Motion was seconded and carried.

The following district presidents' reports were then read:

Auxiliary President's Report—First District

The auxiliary to the First District medical society has held 4 meetings the past year (1954-1955), as is our custom.

We have maintained the same type of meetings as in previous years, with the exception of having held 1 dinner meeting and 3 luncheon meetings. Our first was a dinner meeting at the Gardner Hotel. Our second meeting was a luncheon in November, in honor of our state president, Mrs. Stephen Bacheller. We enjoyed this meeting at the Fargo Country Club, and Mrs. Bigelow, the wife of the director of the Community Theater, entertained us with a monologue by Dorothy Parker. Our third meeting was another luncheon; this was at the Gardner Hotel in December. We had an exchange of Christmas gifts which made it seem quite festive. At this time our financial committee asked the cooperation of the group in each selling 8 tickets for a benefit dessert bridge and fashion show to be held in January. We were all gratified on January 12th when our benefit proved most successful. We held it at the Elks Club and had over 300 guests. We netted $270. This was our first attempt at a project of this type. Our last meeting will be on April 13th.

There are 60 paid-up members in our auxiliary. We feel that we are growing slowly in membership and accomplishment.

We gave $50 to Opportunity School for Handicapped Children. We sold 44 subscriptions to *Today's Health*. Our officers are serving a second year. They are: president, Mrs. L. E. Wold; vice-president, Mrs. R. Rogers; secretary, Mrs. Lee Christoferson; and treasurer, Mrs. Grant Skjelset.

Mrs. L. E. Wold, President

Auxiliary President's Report—Second District

The auxiliary to the Devils Lake District (Second District) medical society held four meetings this past year (1954-55). Bad weather and road conditions held attendance down, but in spite of this quite a lot was accomplished this year. Our membership has increased to 16, and we have decided to hold monthly meetings next year.

This district is listed in *Today's Health* Exclusive Club, which includes districts that make 150 per cent of quota. We have been instrumental in having the district medical society place *Today's Health* in every school and library in the district.

Our members have been active in local community projects. Mrs. I. L. Lazareck was chairman for the mother's march on polio in Devils Lake, and Mrs. L. T. Longmire was residential chairman for the Red Cross drive in Devils Lake.

We were privileged to have Mrs. S. C. Bacheller, state president, as our guest at the November meeting. She gave a very inspirational report on the convention in San Francisco. Mrs. George Loeb, whose husband was the speaker at the men's meeting, was also a guest.

This year our project for the student loan fund was raffling a radio, ticket sales of which netted us $135.25.

Mrs. L. Thomas Longmire, President

Auxiliary President's Report—Third District

The auxiliary to the Grand Forks District Medical Society has held 3 meetings during the year 1954-1955. A fourth meeting is planned for April 20. At that meeting we hope to entertain Mrs. S. O. Bacheller, our state president, and also hold our annual election of officers.

The excellent programs were due to the sound planning of Mrs. E. L. Grinnell. A fine balance was obtained for we enjoyed music and an informative talk on a timely subject at each meeting. In September, Mr. Don Eagles spoke on Blue Cross and Blue Shield. "Therapeutics of Mental Health" was the topic of Dr. Leo B. Forks in November. At our March meeting, Dean E. L. Lium of the University of North Dakota College of Engineering spoke on "Civil Defense." At this same meeting Mr. Amos Martin, secretary of the Grand Forks Chamber of Commerce, discussed the new Air Force jet fighter base projected for the Grand Forks area.

Our main project, the Sophomore Medical Student Loan Fund, has proved to be most successful this year. This is due to the enthusiasm and skill of Mrs. W. C. Dailey, chairman, and Mrs. Frank Hill, cochairman, of our project committee. In November a "Tea and Bake Sale" was held. The net proceeds amounted to $198.31. In February, a benefit valentine supper party was planned for our husbands, at the country club. It was the social highlight of our season. The party was very well supported by the physicians of this area, and the faculty of the school of medicine. This venture raised $553.40. Through the complete cooperation of our members in both activities, our organization has been able to make a contribution of $751.17 to the loan fund.

Our membership in the city of Grand Forks is still

100 per cent. Through the endeavors of Mrs. R. C. Turner, there is now a total paid membership of 61. Of these, 11 live outside the city. This represents an increase in our membership over that of last year.

Auxiliary members again volunteered their services to assist the Cancer Caravan during its visit here. They also volunteered to drive the nurse recruitment teams of the schools of nursing. Our members are constantly aware of the value of good public relations and they participate extensively in a great many civic projects.

New subscriptions and renewals were obtained for the publications *Today's Health* and the *Auxiliary Bulletin*.

Mrs. H. D. Benwell, President

Auxiliary President's Report—Fourth District

As president of the fourth district, I wish to submit the following report:

We have 24 paid-up members and have had 5 meetings this year. The business meetings were preceded by dinner and usually followed by a program.

The executive board appointed committees for the ensuing year at the first meeting, which was held in September. Dues were raised from $5 to $10 to include the student loan fund, the subscription to *The Bulletin* and *Today's Health*. Bill Sullivan, one of our very talented florists, gave a very interesting demonstration on floral arrangement and talked about the care of house plants.

In November, our auxiliary served the fall tea for the Trinity Hospital guild. Mrs. A. R. Sorenson was again chairman for the San Haven Hospital project, which we have sponsored for the past several years, and was in charge of 3 successful sales. Mr. Richard Scheerenberger, supervisor of special education in the Minot schools, gave a talk on "The emotionally disturbed child."

In January, our auxiliary served the St. Joseph's Hospital guild. Mrs. Halliday of Kenmare made arrangements for 2 films to be shown the senior high school girls in Kenmare and Doonybrook high schools to aid the nurse recruiting program. Our state president, Mrs. S. Bacheller, was our guest and speaker.

For the March meeting, Mrs. Halliday was to give a travelogue, but was unable to come because of bad weather. We had as our student loan fund project a food basket, which we passed to our town members, for which the receiver contributed $5. We contributed $200 to the student loan fund.

At the April meeting, election of officers will take place.

Mrs. Paul Breslich, President

Auxiliary President's Report—Fifth District

The Woman's medical auxiliary to the Sheyenne Valley medical society has a membership of 10—and so, perhaps, is the smallest in the state. However, we feel our lack in number is made up for in enthusiasm.

Due to our small membership, we are unable to attempt any big projects. We hold our meetings in homes of the members and expect to wind up the year with a pot luck picnic, which will be held after the state convention and hope to hear reports of it at that time.

We are giving $15 to the scholarship fund and hope we may be able to increase this amount.

Our members are ready and willing to assist in any community projects as they occur.

Grace Meredith, President

Auxiliary President's Report—Sixth District

The Sixth District auxiliary has 54 active members, which is to say that 81 per cent of those eligible are members. This year we lost only 2, and acquired 19 new or reinstated members.

We followed last year's procedure of having our vice-president act as organization and membership chairman. She called or wrote to all eligible non-members prior to our first regualr meeting. Our treasurer followed up with more notes and calls after our first and second meetings, inviting those unable to attend meetings to become dues-paying members.

Pursuant to the suggestion of our organization chairman that we needed some sort of year book to promote interest and understanding, I composed and had mimeographed a memorandum for each paid-up member. This memorandum included a list of officers, chairmen, committees, convention data, tentative program, past presidents and names and addresses of members.

We have had 4 regular dinner meetings. We also had a special luncheon meeting last June to plan our project for the medical student loan fund. Our first regular meeting was in October. Mr. James Swomley, president of the North Dakota Mental Health Association was our program speaker. At our second meeting, in November, our program was social. For our third meeting, in February, our program consisted of a report from our executive secretary, Mr. Lyle Limond, on "Medical Legislation Considered During the Current Legislative Session;" entertainment by 3 students from Connie's Dancing Studio; and Mrs. R. H. Waldschmidt's showing of colored slides of her trip to South America. Our fourth meeting in March was devoted to convention planning, general business and election of officers.

We were happy to have our state officers, Mrs. Bacheller, Mrs. Mahoney, Mrs. Holt, and Mrs. Jansonius visit us in March for a meeting with the chairmen of our various convention committees.

We happily report that we raised $725 for the medical student loan fund, Mrs. R. H. Waldschmidt again acting as our fund-raising chairman ($601.40 was earned through commissions from advance sale tickets for the Miss North Dakota Pageant; $16 was added by raffling of centerpieces at our meetings; $25 was donated by Dr. and Mrs. O. M. DeMoully; and $57.60 is from memorial contributions and convention candy sale proceeds; and another $25 from Dr. and Mrs. Waldschmidt).

Four of our members do Civil Defense work every week at the filter center. Others have had training and have done some work there.

In furthering community health and public relations, most of our members were very active. They worked as volunteers at immunization clinics, in the Mother's March of Dimes, in the Community Chest Drive, at anti-polio vaccine trials, on Cancer Society committees, on Easter Seal sales, at the Annual Art Show, as officers and members of both hospital auxiliaries, and as Girl Scout and Cub Scout leaders. They represented us also at National Foundation for Infantile Paralysis and Community Council meetings. Nine of our members are also members of the North Dakota Mental Health Association.

We collected contributions for the Crusade for Freedom at one of our meetings. One A.M.E.F. memorial gift was given by a group of our members.

Apropos nurse recruitment: 1) we were represented at a state nurse enrollment committee meeting; 2) we reminded the president of the local branch of A.A.U.W. that we would like to have "Nursing as a Career" included in the college night program which A.A.U.W. sponsored at a local high school; 3) we asked some of our members who live in outlying towns in our district to compile a list of any organizations in their towns which are willing to provide scholarships or loans to

students wishing to take nursing training.

We have sold 16 subscriptions to *Today's Health* and 7 subscriptions to the *Bulletin*.

This year, for the first time, we have a historian and a parliamentarian. They have been of much assistance to us.

Because of the fine spirit of service and cooperation shown by our members I can report another year of growth and achievement for the Sixth District auxiliary.

Mrs. Maryruth Heffron, President

Auxiliary President's Report—Seventh District

As president of the Stutsman County Medical Auxiliary of North Dakota, I wish to submit the following report.

This auxiliary consists of 23 members, and during the year we have had 4 meetings.

In May 1954 we entertained the future nurses club, under Sister Carita, and the senior students from the high school and St. John's Academy that were interested in nursing as a career. The instructor from our two schools of nursing spoke briefly. Lunch was served.

Also, in May, we visited doctors' wives in Oaks, LaMoure, Ellendale, and Gackle to interest them in auxiliary work.

In September, the medical auxiliary was asked to sponsor the Nurse's Tag Day, put on by the Central Valley District Nurses' Association. The money collected on this Tag Day is used exclusively for their scholarship fund. This we agreed to do.

On November 8, 1954, the first meeting of the current year was held; a dinner meeting at the Gladstone Hotel. We were very happy to have our state president, Mrs. Stephen C. Bacheller, as our guest. She reported on her June trip to San Francisco, where she attended the A.M.A. convention.

Our Christmas party was held on December 21st, at the home of Mrs. E. J. Larson. Members brought their contributions of food and clothing to be incorporated as part of our donation to the needy family chosen for this year's Christmas basket project.

In March we held our second dinner meeting of the year. Dr. Young of the state hospital spoke to us on mental health.

Our final meeting will be held on April 25th, at which time our officers for 1955-1956 will be elected.

The student loan fund was taken care of by a $5 contribution from each member. A check for $115 was sent to Mrs. C. J. Baumgartner.

Our auxiliary has 22 subscriptions to *Today's Health*.

The members have assisted with Red Cross, cancer, polio, community chest, and other projects when called upon. Mrs. E. J. Larson is county chairman for the cancer drive.

Mrs. Robert L. McFadden, President

Auxiliary President's Report—Eighth District

Our auxiliary which, in the past, has been very small, has grown to 15 members, and we are all in hopes of being able to be more active in the next few years. Last year we had only 2 meetings, the first, our annual election of officers meeting, and the second, to make plans for the state Ob. and Gyn. convention that was held in Williston in September. On the second day of the convention, our auxiliary had a bridge luncheon at the Williston Elks Club for 30 guests.

Last year our auxiliary donated $50, as it has in the previous years, to the student loan fund. Our members have all been very active this past year; also helping with the various health programs, such as: polio drive, blood donors train, cancer caravan, and the Crippled Children's Clinic.

Mrs. E. J. Hagan, President

Auxiliary President's Report—Traill-Steel District

Our 4 informal meetings were held following dinner meetings with our husbands. As you know, our group is primarily social in function, since distances make anything else impossible. Our membership is only 5 this year; some leaving, some retiring, and others wishing to remain absent. We had no special projects as that, too, cannot be accomplished in our group.

Mrs. Keith Vandergon, President

Auxiliary President's Report—Tenth District

The auxiliary to the Southwestern medical society held 4 meetings during the year 1954-1955, meeting on the same evening as the doctors of the district.

It has been the wish of this group to keep on a social basis, so each meeting was a dinner meeting followed by a social get-together at the various homes.

The Southwestern auxiliary has a membership of 21, an increase of 3 members over 1953-1954. This includes wives from Dickinson, Richardton, Bowman, Hettinger, Elgin, Mott, Regeant, Killdeer, and New England.

Our auxiliary increased its contribution to the student loan fund to $63.

Due to a misunderstanding, no subscriptions were sent in for the *Bulletin* this year, but most of our members usually subscribed.

Only one 2 year renewal was sent in for *Today's Health*.

The new officers elected for the coming year are: president, Mrs. Robert Gilliland, and secretary-treasurer, Mrs. Keith Foster.

Mrs. Harlan C. Larsen, President

Motion was made by Mrs. Clyde L. Smith that we accept the district presidents' reports. Motion was seconded and carried.

Mrs. S. C. Bacheller then read the inscription which had been put on the gavel presented to us, in 1954, by Mrs. P. G. Arzt.

Mrs. E. T. Keller moved that we keep the same letterhead on our stationery. After being seconded, motion carried.

Motion was made by Mrs. J. D. Cardy that we send a copy of each of the four *News Letters* to all the doctors' wives in the state. Motion was seconded and carried.

Mrs. S. C. Bacheller read a letter in regard to the crusade for freedom. She then asked whether we should like to make a contribution as an auxiliary or make individual contributions. Mrs. C. A. Arneson made the motion that we make individual contributions. Motion was seconded and carried.

Mr. Lyle A. Limond then introduced Dr. Frank Dickinson, Chicago, Illinois, director of the Bureau of Medical Economics Research of the American Medical Association. He made an appeal to the auxiliary to study the system of "Pensions for Self-Employed Physicians." He advocated legislation that would permit the self-employed and the employed, not covered by pension plans, to set aside from annual income tax deductible amounts which would be taxed in a later year, when withdrawn. He mentioned particularly the Jenkins-Keogh bills, and stated that the American Medical Association had gone on record several times in support of the Jenkins-Keogh bills. He stated that many professional associations are supporting these bills both because of the need for

equitable tax treatment for the self-employed in the accumulation of retirement funds and as a measure to encourage more young professional men to enter the private practice of their professions.

Meeting recessed to reconvene at 2:30 P.M., Municipal Country Club.

A delightful luncheon was held Monday, May 2, at the Municipal Country Club, with Mrs. Clyde L. Smith and Mrs. J. H. Mahoney, president-elect, presiding. Mrs. Smith introduced Mrs. C. A. Arneson, Mrs. Robert Nuessle, Mrs. P. W. Freise, and Mrs. G. D. Icenogle, who were on the luncheon committee.

Mrs. Mahoney gave a few remarks about what our auxiliary should mean to us.

Some very entertaining dance skits were presented by Connie's Dancing Studio.

In the absence of Dr. D. J. Halliday, Mrs. D. J. Halliday gave a very entertaining talk. Mrs. Doris Smith, state advisor of Women's activities for the National Polio Foundation, presented an award to the auxiliary for their support.

The convention reconvened at 2:30 P.M. May 2, 1955. The meeting was called to order by Mrs. S. C. Bacheller, president.

The registration committee reported 85 registrants.

Mrs. Henry Kermott, chairman of the nomination committee, then submitted the following report. President, Mrs. J. H. Mahoney, Devils Lake; president-elect, Mrs. C. A. Arneson, Bismarck; first vice-president, Mrs. J. D. Cardy, Grand Forks; second vice-president, Mrs. V. J. Fischer, Minot; recording secretary, Mrs. J. W. Jansonius, Jamestown; and treasurer, Mrs. A. C. Kohlmeyer, Larimore.

Mrs. Bacheller then asked for nominations from the floor for each of the above offices. As there were none, she declared all the above duly elected and asked the secretary to so record this in the minutes.

Mrs. John M. Van der Linde, Jamestown, was chosen as the delegate to the national convention to be held in Atlantic City in June.

Meeting then adjourned.

A delightful banquet was held Monday, May 2, 6:30 P.M., in the Convention Ball Room of the Patterson Hotel, with Mrs. Milton Berg presiding. Some entertaining numbers were presented by the Bismarck High School choir.

Then, Mrs. Berg introduced our honored guest and speaker, Mrs. Harlan English, Danville,, Illinois, national second vice-president of the Woman's Auxiliary to the American Medical Association.

She started her address by saying no program can be any more important than the cause which brings it into being.

She gave a very interesting history of medicine. She stated that Hippocrates was the first physician to separate from the state, to bring medicine in his own office, and to charge a fee. It was Hippocrates who wrote the code of medical ethics which every physician takes, and also he who followed the exact science which is medicine today.

She compared the problems that physicians had to face in the early history of medicine to our legislative and political problems in medicine today.

She stressed how important it was to us as an auxiliary to work against federal control; that we as doctors' wives must live under the same standards as our husbands, and that the auxiliary offers us a good means of evaluating the problems of medicine.

She mentioned several projects which help us to meet the needs of our profession, namely: American Education Foundation, Civil Defense being well informed and alert, keeping our eyes and ears open to the work of the United Nations, mental health, nurse recruitment, good public relations, and *Today's Health* publications.

In conclusion, she stated that each of us was a tool of the auxiliary, and that we had standards which were set up many years ago, that she wanted each of us to answer that challenge, and have that sense of worth which comes from doing good for America.

Our final business session and social program was a brunch at the Apple Creek Country Club, Tuesday, May 3, at 10:00 A.M. with Mrs. C. A. Arneson, convention chairman, presiding.

Some very interesting skits were presented by Mrs. Paul Johnson.

Mrs. Arneson introduced and thanked the following committee convention chairmen: Mrs. Robert Nuessle co-chairman; Mrs. R. H. Waldschmidt, entertainment; Mrs. W. B. Pierce, transportation; Mrs. H. M. Berg, registration; Mrs. P. W. Freise, table decorations; Mrs. G. D. Icenogle, luncheon; Mrs. T. W. Buckingham, brunch. Mrs. Clyde Smith, press and publicity.

Mrs. V. J. Fischer then read the following proposed budget for 1955-1956:

Income		
Dues 250 members at $3.00	$750.00	
State Medical Association contribution toward auxiliary convention expenses	200.00	
		$950.00
Proposed Expenditures		
President:		
National convention	$250.00	
Chicago conference	100.00	
Discretionary fund	50.00	
Miscellaneous	15.00	
		$415.00
President-elect		
Chicago conference		100.00
Standing committees		25.00
News Letter and stationery		125.00
Miscellaneous		85.00
Convention		200.00
		$950.00

An auditing committee, composed of Mrs. Martin Conroy, Mrs. A. L. Cameron, and Mrs. Henry Kermott was appointed to audit the books by June 30.

The following resolutions reports were then read:

Resolution Report

Whereas, the Woman's Auxiliary of the North Dakota State Medical Association has increased its membership to 295 members; and

Whereas, the Woman's Auxiliary has taken an active leadership in community health and education; and

Whereas, the student loan fund for medical students of the school of medicine at the University of North Dakota has been markedly increased by monies from the Woman's Auxiliary; and

Whereas, the cause of medicine has been bolstered by the auxiliary development of future nurses' clubs, public films, and the promotion of the magazine *Today's Health*:

Now, therefore, be it resolved: that the North Dakota State Medical Association commend the Woman's Auxiliary for their wonderful and valuable work; and

Be it further resolved: that the North Dakota State Medical Association give the Woman's Auxiliary all moral and financial aid possible in strengthening their membership and implementing their programs; and

Be it further resolved, that a copy of this resolution be directed to the President of the Woman's Auxiliary.

Resolution Report—Auxiliary

I.

Be it resolved; that this convention of the Woman's Auxiliary to the North Dakota State Medical Association extend to Mrs. S. C. Bacheller its thanks and sincere appreciation for the great service which she has rendered to that group.

II.

Be it resolved; that the Woman's Auxiliary to the North Dakota State Medical Association express grateful appreciation and thanks to the city of Bismarck, The Woman's Auxiliary to the medical society of the Sixth District, the North Dakota State Medical Association, and the medical society of the Sixth District, the managers and staffs of the hotels, members of the press, radio, and television, Mr. Lyle A. Limond, executive secretary for the North Dakota State Medical Association, Mrs. D. J. Halliday, wife of the incoming president, Dr. P. H. Woutat, Past President, Mrs. Harlan English, national second vice-president, Dr. Frank Dickinson, director of the Division of Economics of the A.M.A., Mrs. Doris Smith, state advisor of Women's Activities for the national foundation for the award she presented to the auxiliary as a whole and to the individual members for services rendered to the national foundation, and all other individuals and groups who contributed to the success of the convention and to the comfort and entertainment of the delegates.

III.

Be it resolved; that the Woman's Auxiliary to the North Dakota State Medical Association express appreciation for the support and cooperation received from all persons, organizations, and agencies who contributed to the success of its program and that of its state and district auxiliaries during the past year.

Mrs. E. J. Beithon, Chairman

Mrs. Gertson moved that the resolutions be adopted. It was seconded and motion carried.

The secretary was instructed to place the resolutions report from the medical society on file.

Mrs. Harlan English then congratulated the incoming officers on their new duties, and installed them in their offices.

Mrs. S. C. Bacheller turned over the files to Mrs. J. H. Mahoney.

Postconvention Minutes

Mrs. J. H. Mahoney called the meeting to order. She stated her theme was going to be: "Be an informed auxiliary member." She was quite enthusiastic about carrying out Dr. Halliday's suggestion in regard to mobile eye clinics.

Mrs. Cardy made a motion that, in revising the awarding of the president's pin, that we revise it to suit the needs of the organization. Motion was seconded and carried.

Mrs. H. M. Berg was appointed chairman to work on the revisions of the constitution and to draw up a new constitution.

Following is a list of officers, committee chairmen, student loan fund committee, district presidents, and district councillors for 1955-1956.

Officers and Committee Chairmen, 1955-1956

President—Mrs. James H. Mahoney, 803 6th St., Devils Lake

President-elect—Mrs. Charles A. Arneson, 714 2nd St., Bismarck

First vice-president—Mrs. James D. Cardy, 3210 5th Ave. N., Grand Forks

Second vice-president—Mrs. V. J. Fischer, 707 3rd St. S.E., Minot

Recording secretary—Mrs. J. W. Jansonius, 609 4th Ave. S.E., Jamestown

Treasurer—Mrs. A. C. Kohlmeyer, Larimore

Committee Chairmen

A.M.E.F.—Mrs. W. E. G. Lancaster, 1332 N. 5th St., Fargo

Bulletin—Mrs. H. L. Kermott, 200 7th Ave. S.E., Minot

Civil defense—Mrs. R. F. Gilliland, 228 9th St. W., Dickinson

Historian—Mrs. D. J. Halliday, Kenmare

Legislation—Mrs. Clyde L. Smith, 622 Raymond, Bismarck

Mental health—Mrs. G. G. Thorgrimsen, 1215 Lincoln Dr., Grand Forks.

Nominating—Mrs. S. C. Bacheller, Enderlin

Nurse recruitment—Mrs. G. N. Vigeland, Rugby

Organization and membership—Mrs. C. A. Arneson, 714 2nd St., Bismarck

Parliamentarian—Mrs. S. C. Bacheller, Enderlin

Press and publicity—Mrs. M. M. Heffron, 320 Ave. B, W., Bismarck

Program—Mrs. James D. Cardy, 3210 5th Ave. N., Grand Forks.

Public relations—Mrs. V. J. Fischer, 707 3rd St. S.E., Minot

Resolutions—Mrs. Martin P. Conroy, 921 1st Ave. S.E., Minot

Rural health—Mrs. John Van Der Linde, 1016 4th Ave. N.E., Jamestown

Revisions—Mrs. H. Milton Berg, 214 Ave. A W., Bismarck

Today's Health—Mrs. Duane Pile, Crosby

Student loan fund committee: Chairman—Mrs. Kenneth E. Fritzell, 1125 Reeves Dr., Grand Forks; Mrs. Carl J. Baumgartner, 615 Washington, Bismarck; Mrs. I. D. Clark, Casselton; Mrs. J. D. Cardy, 3210 5th Ave. N., Grand Forks; Mrs. Joseph D. Craven, 915 2nd Ave. W., Williston

District Presidents

Mrs. V. J. Fischer, 707 3rd St. S.E., Minot; Mrs. Clyde L. Smith, 622 Raymond St., Bismarck; Mrs. James D. Cardy, 3210 5th Ave. N., Grand Forks; Mrs. L. E. Wold, 912 13th St., Moorhead, Minn.; Mrs. J. A. Beall; 510 2nd Ave. N.E., Jamestown; Mrs. Keith J. Vandergon, Portland; Mrs. N. A. MacDonald, 711 5th Ave. N.W., Valley City; Mrs. E. J. Hagen, 804 2nd Ave. E., Williston; Mrs. Robert F. Gilliland, 228 9th St. W., Dickinson; Mrs. Thomas Longmire, 810 6th St., Devils Lake

District Councillors

Mrs. A. L. Cameron, 318 8th Ave. S.E., Minot; Mrs. G. D. Gertson, 511 S. 5th St., Grand Forks; Mrs. C. W. Hunter, 1434 S. 6th St., Fargo; Mrs. R. E. Lucy, 420 4th Ave. S.W., Jamestown; Mrs. Gunder Christianson, 117 N.W. 3rd St., Valley City; Mrs. W. A. Wright, 822 2nd Ave. E., Williston; Mrs. R. W. Rodgers, 146 W. 5th St., Dickinson; Mrs. Ted Keller, Rugby.

Meeting was then adjourned.

1955 MEMBERSHIP ROSTER
WOMAN'S AUXILIARY TO THE NORTH DAKOTA STATE MEDICAL ASSOCIATION

Devils Lake District

Corbett, Mrs. Conner Algernon	316 7th St., Devils Lake
Fawcett, Mrs. John C.	1125 5th St., Devils Lake
Fawcett, Mrs. Robert Magewood	719 4th St., Devils Lake
Fox, Mrs. William Richard	315 Foster Ave. S., Rugby
Gilchrist, Mrs. Milton Roy	Rolla
Hilts, Mrs. George Henry	Cando
Johnson, Mrs. Christian G.	Rugby
Keller, Mrs. Emil Theodore	Rugby
Lazareck, Mrs. Isadore Luke	1032 5th St., Devils Lake
Longmire, Mrs. Lemuel Thomas	810 6th St., Devils Lake
Mahoney, Mrs. James Henry	803 6th St., Devils Lake
Pine, Mrs. Louis Fabien	817 7th St., Devils Lake
Smith, Kathleen (Mrs. Clinton)	Devils Lake
Terlecki, Mrs. Jaroslaw	Minnewaukan
Thordarson, Mrs. John Donald	Maddock
Toomey, Mrs. Glen William	Devils Lake
Vigeland, Mrs. George Norman	Rugby

First District

Amidon, Mrs. B. F.	1325 6th Ave. S., Fargo
Armstrong, Mrs. W. B.	1248 N. 9th St., Fargo
Bacheller, Mrs. S. C.	Enderlin
Barnard, Mrs. Donald	1111 S. 7th St., Fargo
Beithon, Mrs. E. J.	Wahpeton
Beithon, Mrs. Paul	Wahpeton
Bond, Mrs. J. H.	516 S. 13th St., Fargo
Burton, Mrs. P. H.	415 S. 8th St., Fargo
Christoferson, Mrs. Lee	1307 S. 6th St., Fargo
Clark, Mrs. Ira	Casselton
Corbus, Mrs. B. C.	1257 N. 4th St., Fargo
Darrow, Mrs. Kent	716 S. 8th St., Fargo
DeCesare, Mrs. F. A.	1401 S. 9th St., Fargo
Dillard, Mrs. J. R.	620 S. 8th St., Fargo
Fjelde, Mrs. J. H.	1526 S. 8th St., Fargo
Fortin, Mrs. H. J.	1440 S. 8th St., Fargo
Fortney, Mrs. A. C.	1505 S. 12th St., Fargo
Foster, Mrs. G. C.	1513 S. 8th St., Fargo
Gillam, Mrs. J. S.	1433 S. 7th St., Fargo
Gustafson, Mrs. Maynard	1410 S. 5th St., Fargo
Hall, Mrs. G. H.	1250 N. 5th St., Fargo
Hanna, Mrs. J. F.	907 12th Ave. S., Fargo
Heilman, Mrs. Charles	49 18th Ave. N., Fargo
Hunter, Mrs. C. M.	1434 S. 6th St., Fargo
Irvine, Mrs. V. S.	Lidgerwood
Ivers, Mrs. G. U.	1106 S. 10th St., Fargo
James, Mrs. J. B.	1145 10th St. N., Fargo
Jaehning, Mrs. David	Wahpeton
Kiesel, Mrs. Ilmar	Page
Klein, Mrs. A. L.	1441 S. 9th St., Fargo
Koons, Mrs. Wilbur	Lidgerwood
Lancaster, Mrs. W. E. G.	1332 N. 5th St., Fargo
Landa, Mrs. Marshall	1335 S. 6th St., Fargo
Larson, Mrs. G. A.	1538 S. 9th St., Fargo
LeBien, Mrs. Wayne	1353 N. 5th St., Fargo
LeMar, Mrs. John D.	1324 N. 5th St., Fargo
Lewis, Mrs. A. K.	Lisbon
Lewis, Mrs. T. H.	1502 S. 6th St., Fargo
Long, Mrs. W. H.	1438 S. 8th, Fargo
Macaulay, Mrs. W. L.	1410 S. 9th, Fargo
Mazur, Mrs. B. A.	1237 N. 3rd, Fargo
Melton, Mrs. F. M.	1545 S. 6th, Fargo
Miller, Mrs. H. H.	Wahpcton
Nichols, Mrs. W. C.	1449 S. 10th, Fargo
Poindexter, Mrs. M. H.	1350 S. 9th, Fargo
Pray, Mrs. L. G.	1526 S. 7th, Fargo
Rogers, Mrs. R. G.	1217 S. 7th, Fargo
Schleinitz, Mrs. F. B.	Hankinson
Sedlak, Mrs. O. A.	1019 S. 9th, Fargo
Skjelset, Mrs. A. G.	1018 S. 10th, Fargo
Stafne, Mrs. W. A.	1409 S. 9th, Fargo
Swanson, Mrs. J. C.	1220 S. 8th, Fargo
Urenn, Mrs. B. M.	1005 S. 9th, Fargo
Veitch, Mrs. Abner	Lisbon
Webster, Mrs. W. O.	823 S. 14th, Fargo
Weible, Mrs. R. D.	1628 S. 9th, Fargo
Weible, Mrs. R. W.	1630 S. 9th, Fargo
Wold, Mrs. L. E.	912 S. 13th, Moorhead, Minn.
Zauner, Mrs. Richard	1005 N. 13th Ave., Fargo

Grand Forks District

Arneson, Mrs. A. O.	419½ S. 5th St., Grand Forks
Benson, Mrs. Theodore Q.	1524 Walnut, Grand Forks
Benwell, Mrs. Harry D.	625 S. 3rd St., Grand Forks
Berger, Mrs. Phil R.	7 Euclid Ave., Grand Forks
Boynton, Mrs. Bruce	935 Kittson Ave., Grafton
Campbell, Mrs. R. D.	323 S. 6th St., Grand Forks
Cardy, Mrs. James D.	1110 Reeves Drive, Grand Forks
Chasten, Mrs. Stephen M.	1101 Reeves Drive, Grand Forks
Countryman, Mrs. George L.	Grafton
Culmer, Mrs. A. E., Jr.	101 Reeves Court, Grand Forks
Dailey, Mrs. Walter C.	1118 Reeves Drive, Grand Forks
Deason, F. W.	Box 348, Grafton
Delano, Mrs. Robert	Northwood
Flaten, Mrs. A. N.	Edinburg
Fritzell, Mrs. Kenneth E.	1125 Reeves Drive, Grand Forks
Froke, Mrs. Leo	621 S. 5th St., Grand Forks
Gertson, Mrs. G. D.	511 S. 5th, Grand Forks
Goehl, Mrs. Reinhold O.	1015 Reeves Drive, Grand Forks
Graham, Mrs. Charles N.	923 Almonte Ave., Grand Forks
Graham, Mrs. John H.	1523 Cottonwood Ave., Grand Forks
Grinnell, Mrs. Ernest L.	1207 Lincoln Drive, Grand Forks
Harwood, Mrs. Theodore H.	Belmont Road, Grand Forks
Haugen, Mrs. C. O.	Box 436, Larimore
Haunz, Mrs. Edwin A.	1029 Lincoln Drive, Grand Forks
Hill, Mrs. Frank	812 Letnes Drive, Grand Forks
Hofto, Mrs. J. M.	321 N. 4th St., Grand Forks
Jensen, Mrs. August F.	1721 Belmont Road, Grand Forks
Kohlmeyer, Mrs. A. C.	Larimore
Landry, Mrs. L. H.	Walhalla
Leigh, Mrs. James A.	606 N. 3rd, E. Grand Forks
Leigh, Mrs. Ralph E.	301 Park Ave., Grand Forks
Liebeler, Mrs. Wilbert W.	South Washington, Grand Forks
Lommen, Mrs. C. E.	Fordville
Mahowald, Mrs. Ralph E.	606 S. 5th St., Grand Forks
Moore, Mrs. John	1114 Reeves Drive, Grand Forks
Mulligan, Mrs. Thomas	514 Belmont Road, Grand Forks
Muus, Mrs. O. Harold	59 4th Ave. So., Grand Forks
Nelson, Mrs. Wallace W.	511 17th Ave. S., Grand Forks
Painter, Mrs. Robert C.	1121 Belmont Road, Grand Forks
Panek, Mrs. A. F.	Milton
Papenfuss, Mrs. Harlan L.	3220 5th Ave. N., Grand Forks
Pettit, Mrs. Sam	Rhinehart Drive, E. Grand Forks
Porter, Mrs. Charles B.	1210 Chestnut Ave., Grand Forks
Potter, Mrs. W. F.	2024 2nd Ave. N., Grand Forks
Prochaska, Mrs. L. J.	412 S. 6th, Grand Forks
Quale, Mrs. Victor S.	1620 Belmont Road, Grand Forks
Ralston, Mrs. Lloyd S.	2612 5th Ave. N., Grand Forks
Revere, Mrs. Jack W.	714 Maple Ave., Grand Forks
Ruud, Mrs. Henry O.	1404 Chestnut Ave., Grand Forks
St. Clair, Mrs. Robert T.	919 Letnes Drive, Grand Forks
Sandmeyer, Mrs. John A.	1005 Lanark Ave., Grand Forks
Silverman, Mrs. Louis B.	626 Belmont Road, Grand Forks
Stratte, Mrs. Joseph J.	403 Division St., Grand Forks
Strom, Mrs. Adrian D.	Langdon
Talbert, Mrs. Myron J.	509 S. 3rd St., Grand Forks
Thorgrimsen, Mrs. G. G.	1215 Lincoln Drive, Grand Forks
Turner, Mrs. Robert C.	1120 Cottonwood St., Grand Forks
Witherstine, Mrs. William H.	214 8th Ave. S., Grand Forks
Woutat, Mrs. P. H.	1205 Lincoln Drive, Grand Forks
Youngs, Mrs. Nelson A.	511 Reeves Drive, Grand Forks

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Craven, Mrs. John P.	403 3rd Ave. E., Williston
Craven, Mrs. Joseph D.	915 2nd Ave. W., Williston
Ellis, Mrs. G. E.	602 14th Ave. W., Williston
Hagan, Mrs. Edward J.	904 2nd Ave. E., Williston
Hagan, Mrs. Joan G.	410 2nd Ave. E., Williston
Johnson, Mrs. Alan K.	1004 4th Ave. E., Williston
Korwin, Mrs. Justin J.	701 2nd Ave. E., Williston
Lund, Mrs. C. M.	701 1st Ave. E., Williston
McPhail, Mrs. C. O.	Crosby
Pile, Mrs. Duane F.	Crosby
Sathe, Mrs. A. G.	1205 6th Ave. E., Williston
Skjei, Mrs. Donald E.	623 3rd Ave. W., Williston
Strinden, Mrs. D. E.	1029 1st Ave. E., Williston
Wright, Mrs. W. A.	822 2nd Ave. E., Williston

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Cameron, Mrs. Angus L.	318 8th Ave. S.E., Minot
Clark, Mrs. Joseph H.	625 5th St. S.E., Minot
Conroy, Mrs. Martin P.	821 1st Ave. S.E., Minot
Devine, Mrs. John L., Jr.	901 4th St. S.E., Minot
Dormont, Mrs. Richard E.	202 9th St. S.E., Minot
Fischer, Mrs. V. J.	707 3rd St. S.E., Minot
Gammell, Mrs. Robert T.	Kenmare

Garrison, Mrs. M. W.	612 Mount Curve S.E., Minot
Girard, Mrs. B. A.	Mohall
Goodman, Mrs. Robert	Powers Lake
Halliday, Mrs. David J.	Kenmare
Hart, Mrs. George M.	912 2nd St. N.W., Minot
Hoopes, Mrs. Lorman L.	118 9th Ave. S.E., Minot
Hordinsky, Mrs. Bohdan Z.	Drake
Huntley, Mrs. W. B., Jr.	208 7th Ave. S.E., Minot
Kermott, Mrs. L. Henry, Jr.	200 7th Ave. S.E., Minot
Kitto, Mrs. William	1021 Central Ave. W., Minot
McArdle, Mrs. John S.	1431 1st St. S.E., Minot
McCannel, Mrs. Archibald D.	505 Main St. S., Minot
Olson, Mrs. Burton G.	629 3rd St. S.E., Minot
Shea, Mrs. Samuel	808 1st St. S.E., Minot
Sorenson, Mrs. A. R.	114 6th St. S.E., Minot
Sorenson, Mrs. Roger	900 1st St. S.E., Minot
Uthus, Mrs. Oliver S.	703 4th St. S.E., Minot
Veenbaas, Mrs. Fred J.	219 4th Ave. S.E., Minot

Sheyenne Valley District

Brown, Mrs. Frederick	466 4th Ave. S.W., Valley City
Christianson, Mrs. Gunder	117 N.W. 3rd St., Valley City
Crosby, Mrs. E. B.	132 Central Ave. S., Valley City
Gilsdorf, Mrs. W. H.	222 3rd Ave. S.E., Valley City
Klein, Mrs. Clifford J.	260 N.W. 6th St., Valley City
Macdonald, Mrs. A. C.	607 5th Ave. N.W., Valley City
Macdonald, Mrs. Neil A.	711 5th Ave. N.W., Valley City
Meredith, Mrs. Charles J.	700 Chautauqua Blvd., Valley City
Merrett, Mrs. J. P.	479 3rd Ave. N.W., Valley City
Wicks, Mrs. Fred L.	726 Chautauqua Blvd., Valley City

Sixth Dsitrict

Arneson, Mrs. Charles A.	714 N. 2nd St., Bismarck
Baumgartner, Mrs. Carl J.	615 N. Washington, Bismarck
Berg, Mrs. H. Milton	214 Ave. A W., Bismarck
Blumenthal, Mrs. Philip	107 First Ave. N.W., Mandan
Boerth, Mrs. Edwin H.	825 Griffin N., Bismarck
Brink, Mrs. Norvel O.	212 Ave. F W., Bismarck
Buckingham, Mrs. Tracy W.	1030 5th St. N., Bismarck
Cartwright, Mrs. John T.	926 7th St. N., Bismarck
Dahl, Mrs. Philip O.	1111 S. Highland Acres, Bismarck
Davidson, Mrs. Hugh	Riverdale
DeMoully, Mrs. Oliver	Flasher
Diven, Mrs. Wilbur	119 Ave. B W., Bismarck
Enders, Mrs. W. R.	Hazen
Eriksen, Mrs. Johan	315 East Park, Bismarck
Fredricks, Mrs. Leonard H.	112 Ave. B W., Bismarck
Freise, Mrs. Paul W.	831 Mandan St. N., Bismarck
Gaebe, Mrs. O. C.	New Salem
Gregware, Mrs. Roy	1107 S. Highland Acres Road, Bismarck
Gutowski, Mrs. Franz	Wishek
Harrington, Mrs. James	107 1st Ave. N.W., Mandan
Heffron, Mrs. Maurice M.	320 Ave. B W., Bismarck
Henderson, Mrs. R. W.	1028 N. 4th St., Bismarck
Hetzler, Mrs. A. E.	602 6th Ave. N.W., Mandan
Icenogle, Mrs. Grover D.	232 Ave. C W., Bismarck
Jacobson, Mrs. Melvin S.	Elgin
Johnson, Mrs. Kenneth J.	211 Cheyenne Ave., Bismarck
Johnson, Mrs. M. J. E.	518 Ave. A W., Bismarck
Johnson, Mrs. Paul L.	220 Ave. A W., Bismarck
Kling, Mrs. Robert	1449 12th St. N., Bismarck
Kuplis, Mrs. Harold	Turtle Lake
LaRose, Mrs. V. J.	712 N. Mandan St., Bismarck
Larson, Mrs. Leonard W.	219 Ave. B W., Bismarck
Lipp, Mrs. George R.	502 W. Rosser, Bismarck
Mears, Mrs. Edward J.	1124 N. 4th St., Bismarck
Nickerson, Mrs. Evelyn	309 5th Ave. N.W., Mandan
Nuessle, Mrs. Robert F.	106 Ave. D, Bismarck
Nugent, Mrs. Milton	929 Riverview, Bismarck
Orr, Mrs. August C.	922 N. 9th St., Bismarck
Owens, Mrs. P. L.	1214 N. 4th, Bismarck
Peters, Mrs. Clifford	805 N. Griffin, Bismarck
Pierce, Mrs. Willard B.	911 Ave. C W., Bismarck
Ramstad, Mrs. N. O.	824 N. 4th St., Bismarck
Saxvik, Mrs. R. O.	Box 476, Jamestown
Schoregge, Mrs. Charles	507 N. 6th St., Bismarck
Schoregge, Mrs. Robert D.	1420 Ave. E, Bismarck
Smith, Mrs. Cecil C.	506 N.W. 3rd, Mandan
Smith, Mrs. Clyde L.	622 Raymond, Bismarck
Thompson, Mrs. Arnold M.	610 Ave. A W., Bismarck
Tudor, Mrs. Robert B.	714 Ave. C W., Bismarck
Vinje, Mrs. Ralph	916 Ave. C W., Bismarck
Waldschmidt, Mrs. Rueben H.	600 N. Washington, Bismarck
Walter, Mrs. Eric W.	1028 N. 11th St., Bismarck
Wittchow, Mrs. Allen W.	1413 N. 12th St., Bismarck
Zukowsky, Mrs. Anthony	Steele

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DePuy, Mrs. Thomas L.	301 2nd Ave. S.E., Jamestown
Elsworth, Mrs. John N.	605 5th St. N.E., Jamestown
Fergusson, Mrs. V. D.	Edgeley
Freeman, Mrs. John	State Hospital, Jamestown
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Hogan, Mrs. Clifford	306½ 4th Ave. N.E., Jamestown
Holt, Mrs. George H.	214 2nd Ave. S.W., Jamestown
Jansonius, Mrs. John W.	609 4th Ave. S.E., Jamestown
Kooiker, Mrs. Robert	502 3rd Ave. S.W., Jamestown
Kuisk, Mrs. Hans	Rutland
Larson, Mrs. Ernest J.	321 2nd Ave. S.E., Jamestown
Lucy, Mrs. Robert E.	420 4th Ave. S.W., Jamestown
McFadden, Mrs. Robert E.	910 3rd Ave. N.W., Jamestown
Nierling, Mrs. Richard D.	415 9th St. S.E., Jamestown
Pederson, Mrs. Thomas D.	416 4th Ave. N.E., Jamestown
Place, Mrs. B. A.	State Hospital, Jamestown
Sorkness, Mrs. Joseph	318 3rd Ave. S.E., Jamestown
Van Der Linde, Mrs. J. M.	1016 4th Ave. N.E., Jamestown
Van Houten, Mrs. R. W.	Oakes
Woodward, Mrs. Robert S.	310 10th Ave. N.E., Jamestown
Woodward, Mrs. Floyd O.	722 3rd St. N.E., Jamestown

Traill-Steele District

Knutson, Mrs. O. A.	Buxton
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McLean, Mrs. Robert W.	Hillsboro
Mergens, Mrs. Daniel N.	Hillsboro
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Southwestern District

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Buckingham, Mrs. William	Elgin
Curiskis, Mrs. A. A.	New England
Dukart, Mrs. C. R.	208 4th Ave. W., Dickinson
Dukart, Mrs. Ralph	443 1st Ave. E., Dickinson
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Gilliland, Mrs. Robert	446 1st Ave. W., Dickinson
Guloien, Mrs. Hans E.	41 5th Ave. W., Dickinson
Gumper, Mrs. A. J.	7 E. 4th, Dickinson
Hankins, Mrs. Robert	Mott
Hill, Mrs. Simon	Regent
Larsen, Mrs. Harlan C.	730 W. 1st, Dickinson
Martens, Mrs. A. A.	Bowman
Moses, Mrs. James	Richardton
Natchwey, Mrs. A. P.	115 5th Ave. W., Dickinson
Reichert, Mrs. Donald	24 Villard, Dickinson
Reichert, Mrs. Larry	543 1st Ave. W., Dickinson
Rodgers, Mrs. Robert W.	146 W. 6th, Dickinson
Smith, Mrs. Oscar	509 1st Ave. W., Dickinson
Spear, Mrs. A. E.	610 1st Ave. W., Dickinson

American College Health Association News . . .

The following schools have been dropped from the membership rolls of the American College Health Association as of July 1, 1955: Kentucky State College, Frankfort, Kentucky; Queen's University, Kingston, Ontario, Canada; and South Dakota State College, Brookings. As instructed by the membership at the business meeting in Colorado Springs in May 1955, the presidents of the above colleges were notified of the deliquency of their schools on May 18, 1955.

R. Y. Chapman, dean of student personnel, informed the secretary-treasurer in a letter of May 23, 1955, that South Dakota State College had decided to discontinue membership in the Association for the present. As no reply has been received from the administrators, Kentucky State University and Queen's University are also being stricken from the membership roster.

At the business meeting in Colorado Springs, both council and members recommended that all local sections send papers and reports of merit from their local section meetings to *Student Medicine* for possible publication in that journal. Norman S. Moore, M.D., and the editorial staff of *Student Medicine* at Cornell University feel that if some of the interesting material from local section meetings is made available to them, *Student Medicine* can be published quarterly rather than semi-annually, as at present.

PERSONNEL

Morley Beckett, M.D., has been appointed by the University of Michigan Board of Regents to succeed Warren Forsythe, M.D., as director of the Student Health Service. Dr. Forsythe retired on June 30, 1955, after thirty-eight years in student health work.

Dr. Beckett is a graduate of the University of Toronto Medical School and received the degree of M.P.H. from Johns Hopkins University in 1953. After a year on the administrative staff of University Hospital in Ann Arbor in 1946, he became director of the Royal Jubilee Hospital, Vancouver Island, B. C., then manager of the Veteran's Hospital in Saginaw, Michigan, then director of activities for the Kellogg Foundation in Battle Creek, and finally, in 1953, director of the Veteran's Hospital in Ann Arbor. He leaves this post to assume the directorship of the Student Health Service at the University of Michigan.

Ben H. McConnell, M.D., of Beltsville, Maryland, has been appointed director of student health at Denison University, Granville, Ohio as of September 1, 1955. President A. Blair Knapp of Denison University, in writing the Secretary of the appointment, sent his thanks to the Association for the assistance received from the ACHA office in filling the vacancy.

John M. Stevens, Jr., M.D., is the newly-appointed psychiatrist on the staff of the Health Service of the University of Pennsylvania, Philadelphia. Dr. Stevens has been a member of the staff of Pontiac State Hospital, Pontiac, Michigan, for the past several years. Starting with September, he will devote full time to his new position.

The Journal Lancet
SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

Certain Pathologic Features of Carcinoma of the Stomach

MALCOLM B. DOCKERTY, M.D.
Rochester, Minnesota

Carcinoma of the stomach snuffs out the lives of almost 40,000 people in the United States of America each year. With the best current methods of treatment, only about 15 per cent of these lives could have been saved. In the present state of ignorance concerning the cause of this disease, physicians seem able to do little by way of reducing the high incidence of the condition. Can an inquiry into its pathologic aspects discern ways and means of improving the present poor rate of salvage?

The material to be presented is based on studies carried out on surgically resected stomachs at the Mayo Clinic. The carcinomas concerned were early in the sense that they were removable and for the most part they represented resections performed with hope of cure. The following observations with regard to their gross and microscopic features may give some enlightenment as to why the original hope was realized in only 30 per cent of cases.

TYPES OF GASTRIC CARCINOMA

Ulcerative adenocarcinoma. About 60 per cent of resected gastric carcinomas show shallow or deep ulcerations on their mucosal surfaces. Since they involve chiefly the lower half of the stomach, free hydrochloric acid will be present in the gastric contents in almost half the cases. The lesions vary from 3 to 10 cm. in diameter and have raised edges and necrotic bases; 80 per cent of them have a plainly "malignant look."

Of greater interest are the lesions that are less than 2.5 cm. in diameter and that have undergone deep peptic digestion. With regard to such lesions, the history, the results of gastric analysis, the roentgenologic appearance, the surgical findings, and the gross picture in the laboratory are frequently those of benign peptic ulcer. Yet these lesions microscopically are carcinomas and 15 per cent of them have spread to the regional lymph nodes. The operative mortality rate after their removal is the same as that for benign peptic ulcer and the five-year survival rate approaches 60 per cent. Whether or not they began as ulcers is completely beside the point. The fact remains that gastric carcinomas masquerading as peptic ulcers make up a sizable group in which good results can be achieved.

In a parallel study, Dr. Cain, one of my colleagues, followed a large group of patients whose gastric ulcers responded so favorably to medical management that the consulting surgeons were impressed to the extent of sending the patients home minus abdominal incisions. Carcinoma of the stomach developed in exactly 10 per cent of these patients.

To any conscientious pathologist, every gastric ulcer is malignant until its benign nature is proved microscopically. We are particularly suspicious of prepyloric ulcers and those situated

MALCOLM B. DOCKERTY, *a 1934 graduate of Dalhousie University Faculty of Medicine, is with the section of surgical pathology at the Mayo Clinic, Rochester.*

Read at the meeting of the North Dakota State Medical Association, Bismarck, North Dakota, April 30 to May 3, 1955.

along the greater curvature. On the other hand, deeply penetrating ulcers on the posterior wall are rarely malignant even when they are large.

Polypoid carcinoma. About 10 per cent of gastric carcinomas are bulky or polypoid. Yet, in spite of their large average size, they carry a better outlook than do the ulcerative lesions. Polypoid growths tend to originate in the upper portion of the stomach and achlorhydria is a frequent accompaniment. Since this is the type frequently encountered in pernicious anemia, I should like to discuss this peculiar pathologic combination.

Carcinoma of the stomach is the lesion present in 75 per cent of all pernicious-anemia patients who have carcinoma. About 100 patients with a combination of pernicious anemia and gastric carcinoma have been seen at the clinic. The diagnosis of pernicious anemia was made first in 60 per cent of these patients, whereas both conditions were found simultaneously in 25 per cent and carcinoma was the first condition observed in the remainder. This combination was rare before 1929, when liver therapy became available and allowed these anemic patients to reach the "cancer age."

About 65 per cent of these carcinomas associated with pernicious anemia were situated in the upper reaches of the stomach. This percentage is in contrast to ulcerative adenocarcinoma, 70 per cent of which involve the distal half of the stomach. Of the lesions, 50 per cent were resectable, 30 per cent were multiple, a figure 10 times greater than that found in any control series. Stages of transition from hyperplastic glands were found peripherally in the flattened zones of so-called atrophic gastritis. Polyps were encountered in 8 per cent. The average grade of malignancy of these carcinomas was lower than that found in a control series and, in spite of the large size of the lesions, they afforded a reasonably good prognosis.

Scirrhous carcinoma. This type comprises 10 per cent of gastric carcinomas and is characterized by a pronounced fibrotic reaction that, in its extensive form, produces the typical leather bottle stomach. Most of these lesions are nonresectable. A study was made at the clinic by Dr. Skroch on almost 100 patients who had this type of neoplasm. The five-year survival rate among patients whose stomachs were resected with hope of cure was only 3 per cent. Scirrhous carcinoma is the most serious form of gastric malignant lesions.

Mucous carcinoma. Carcinoma of the stomach arises from mucus-producing cells and many malignant tumors of the stomach are grossly gelatinous. These lesions apparently have a pronounced tendency toward transcelomic spread with the production of "rectal-shelf" lesions and Krukenberg's tumors.

Carcinoma en nappe. This is a rarely reported type of gastric carcinoma in which large portions of the gastric mucosa show superficial in situ carcinoma. A lesion of this type has been known to involve the entire length of the stomach from the esophagus to the duodenum.

SPREAD OF GASTRIC CARCINOMA

Carcinoma of the stomach spreads by direct extension through lymphatic vessels via portal blood radicles and by peritoneal sedimentation. Little can be done about the last-named process, but gastric carcinoma sometimes can be cured after it has begun to spread by the other routes. Many gastric carcinomas are irremovable because of direct infiltration of surrounding tissues and organs. A number of workers correctly point out, however, that resection of multiple organs is indicated in some of these cases because the fixation may be on an inflammatory basis. The surgical pathologist examining a gastric carcinoma that has perforated into the transverse colon actually may not find any evidence of nodal involvement. Invasion of the duodenum can be found microscopically in 30 per cent of lesions that abut on the pylorus. In a series studied earlier at the clinic, such involvement reached the actual line of transection in 50 per cent of cases and bad results more than confirmed this fact. At least 2.5 cm., and preferably more, of the duodenum should be sacrificed in these situations. Recurrence in the gastric remnant, found in as many as 50 per cent of necropsies by various workers, probably also reflects direct spread in the gastric wall in cases in which the surgeon had resected too closely to the gross upper edge of the lesion.

Spread by way of blood vessels is, of course, serious. Hepatic involvement, observed in 30 per cent of cases at laparotomy, generally contraindicates resection of the stomach.

The important gastric chains of lymph nodes are involved by metastatic carcinoma in 60 per cent of cases and such involvement reduces the five-year survival rate from 60 per cent to less than 15 per cent after resection.

Working in our laboratory, Dr. ReMine studied a group of 35 patients who had gastric carcinoma involving the lymph nodes who lived for more than five years. He compared them with a second group of 35 patients who likewise had nodal spread but who all died within one year after operation. The short-term survivors had

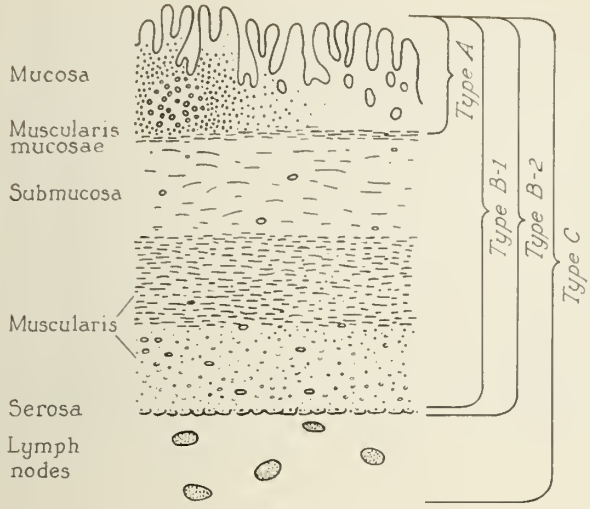

Fig. 1. Diagram showing one method of measuring degree of spread of gastric carcinoma. (Reproduced with the kind permission of the publisher from Dochat, G. R., and Gray, H. K.: Carcinoma of the stomach: prognosis based on a combination of Dukes' and Broders' method of grading. Am. J. Clin. Path. 13: 441-449, 1943.)

pyloric obstruction twice as often and annular lesions 3 times as often as did the long-term survivors. The short-term survivors had metastatic invasion of the lymph nodes on both curvatures 3 times as frequently as did the long-term survivors. Most important, the incidence of invasion of the subpyloric nodes was 12 times as great in the former group. Nodes containing metastatic carcinoma that are located more than 2.5 cm. from the nearest margin of the primary growth bode ill for the patient.

An almost-forgotten group of nodes is that cluster residing in the hilus of the spleen. Dr. Fly recently investigated this group at the clinic and found, to our mutual amazement, metastasis to these nodes in more than 30 per cent of cases; 20 per cent of gastric lesions primary in the lower reaches of the stomach involved splenic hilar nodes. Since the spleen is not essential to life, the implications of this study are obvious.

A convenient way of measuring degrees of spread in operable gastric carcinoma is to apply a modification of Dukes' classification to these growths (figure 1). Dr. Dochat carried out such a study in this laboratory with the following results in regard to prognosis: Lesions involving the mucosa only (type A) were associated with a 100 per cent five-year survival rate. Those extending through to the peritoneum (type B) showed a 44 per cent five-year survival rate. Lesions that had spread to the lymph nodes (type C) were associated with a five-year survival rate of only 15 per cent.

Another method of classifying gastric carcinoma consists in grading the lesions microscopically by the Broders method. According to this scheme, 98 per cent of gastric carcinomas are adenocarcinomas, with varying degrees of success in the attempt of the cells to line up around glandular spaces (figures 2 and 3). Survival rates according to this mode of classification are shown in figure 4. Cancer of the stomach is serious because nearly all the lesions are anaplastic. Thus, grade 3 or grade 4 lesions predominate, as measured by the Broders method.

OTHER TYPES OF GASTRIC MALIGNANT LESIONS

Space does not permit detailed consideration of several other types of gastric malignant lesions, such as carcinoids, teratomas, and squamous cell carcinomas. However, mention should be made of a lesion that carries a good prognosis in spite of an appearance that is ominous both grossly and microscopically. When a surgeon encounters a gastric malignant tumor that is larger than a dinner plate and yet is still movable, the growth

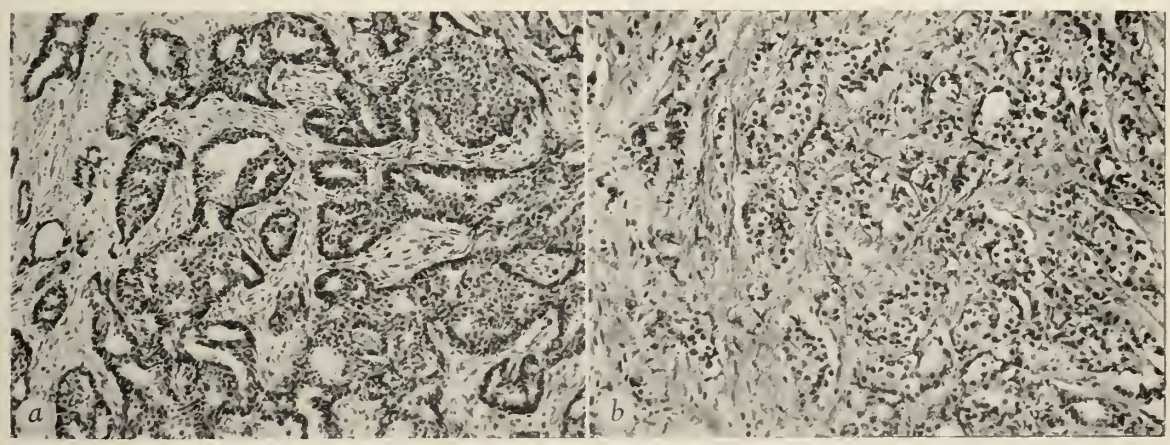

Fig. 2*a*. Adenocarcinoma grade 1; note good cellular differentiation, with reproduction of glandular spaces resembling the normal. *b*. Adenocarcinoma grade 2; the glandular differentiation is less perfect than that shown in *a* and the component cells show a greater departure from their columnar character in the normal mucosal lining.

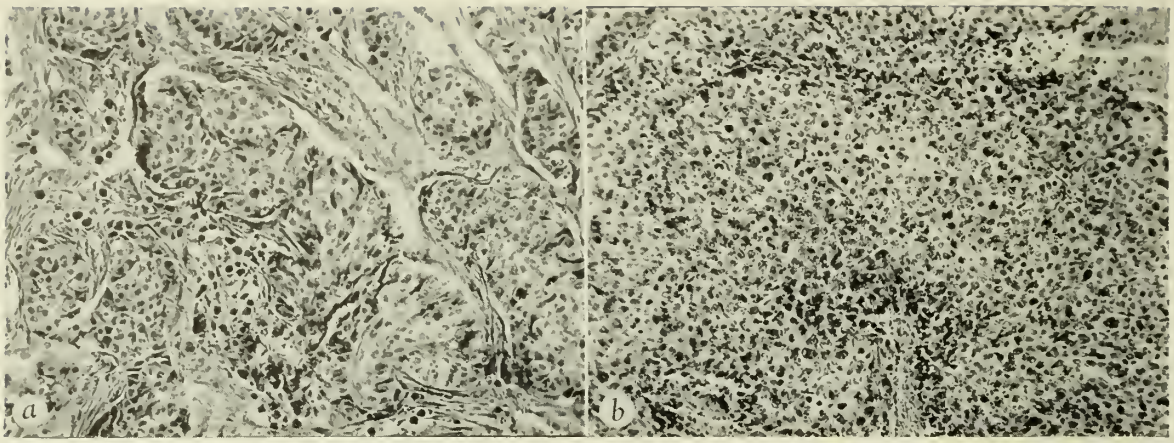

Fig. 3*a*. Adenocarcinoma grade 3; alveolar grouping along with the presence of an occasional glandular space typifies this advanced degree of cellular dedifferentiation. *b*. Adenocarcinoma grade 4; anaplasia is so pronounced that even imperfectly formed glands may be difficult to find.

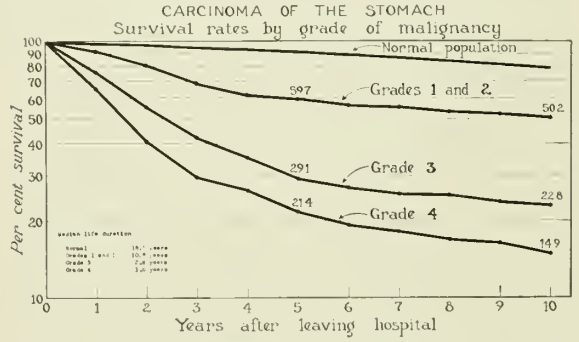

Fig. 4. Correlation of grades of malignancy of gastric carcinoma with postoperative survival of patients. (Reproduced, with modifications and with the kind permission of the publisher, from Walters, Waltman, Gray, H. K., and Priestley, J. T.: Carcinoma and Other Malignant Lesions of the Stomach. Philadelphia: W. B. Saunders Co., 1943. 576 pages.

is most likely to be a primary gastric lymphosarcoma. It should be resected in spite of metastatic involvement of nodes and roentgen therapy should be given postoperatively. If the lesion is irremovable, biopsy should be done to establish the diagnosis. If lymphosarcoma is found, large doses of roentgen rays should be administered. Cure of resectable lesions of this type approaches a rate of 60 per cent. I know of 3 instances in which five-year survivals were achieved from use of roentgen therapy alone. These lymphosarcomas comprise less than 2 per cent of malignant gastric tumors but, in the treatment of malignant disease of this organ, an additional salvage of even 1 per cent is a major achievement.

SUMMARY

Gastric carcinoma is serious because of its frequency, its manifest anaplasia, and its tendency toward early spread. Successful treatment is predicated on early diagnosis, the best results being achieved in the group of patients whose lesions mimic peptic ulcer.

Patients who have pernicious anemia, atrophic gastritis and achlorhydria, or gastric polyps are potential candidates for the development of gastric carcinoma and should be carefully watched.

Surgical resection for this disease should be wider than it has been in relation to the duodenum, subpyloric lymph nodes, and the spleen, which, along with its hilar group of nodes, should be added to the tissue sacrificed.

An extremely large primary lesion should not be a deterrent to resection, since a number of such large growths are lymphosarcomas, which frequently can be cured. To give the roentgen therapist his occasional chance for success in the treatment of these rare lesions, biopsy is always compulsory when the tumor cannot be removed.

Pediatric Implications of Recent Research in Porphyrin Metabolism

ROBERT A. ALDRICH, M.D.
Portland, Oregon

PORPHYRIN-DERIVED compounds in plants—chlorophylls—and in animals—hemes—participate in two key mechanisms, the utilization of the sun's energy through photosynthesis and the formation of energy from organic substances by cellular respiration. After nearly a century, the subject of porphyrin metabolism has moved from the purely descriptive phase into an era where clinical features of human porphyria and the porphyrinurias may soon be explained in terms of known chemical mechanisms. This evolution has been recorded through the years by excellent reviews.[1–10] The porphyrias are fine examples of genetically determined metabolic errors which lend themselves to fundamental research on the nature and function of porphyrin-containing compounds.[2,10–12]

The heme pigments, which include hemoglobin, myoglobin, catalase, and the cytochromes, are formed from an iron-protoporphyrin complex attached to a specific protein.[13] They are located intracellularly and perform functions vital to the transport, storage, and utilization of oxygen. My purpose is to point out some recent findings in the porphyrin field which may lead us to the true causes of altered porphyrin metabolism in a variety of clinical conditions.

HUMAN PORPHYRIA

There are two principal varieties of human porphyria. Each has its distinctive clinical and biochemical pattern centering on one hand in the bone marrow (porphyria erythropoietica), and on the other in the liver (porphyria hepatica).[14,15] The former is rare, usually being noted for the first time during infancy or early childhood. The latter is more common and limited almost exclusively to adults, but both are considered to be inborn errors of metabolism.[2,4,10,16] Porphyria hepatica may represent a trait which is unmasked after adolescence by several factors, some of which are still unknown.

1. *Porphyria erythropoietica.*[1,2,10,14,15] This exceedingly rare but historically important form of porphyria occurs in early childhood. It is characterized clinically by skin photosensitivity, splenomegaly, hemolytic anemia, erythrodontia, hypertrichosis, and red-colored urine. Coproporphyrin and uroporphyrin isolated from the urine and feces are type I isomers for the most part, but in some instances type III porphyrin has also been identified. These children show neither the porphyrin-zinc complex nor the monopyrrole, porphobilinogen, in their excreta. Bone marrow preparations show normoblastic hyperplasia.[10,14,15] The red fluorescence of coproporphyrin and uroporphyrin can be localized by fluorescence microscopy in the nuclei and to a lesser extent the cytoplasm of normoblasts.[15] It is noteworthy that some normoblasts show no fluorescence, which suggests that there are two populations. In view of the higher porphyrin concentration in bone marrow as compared to circulating erythrocytes, the conclusion may be reached that the uroporphyrin and coproporphyrin in plasma and the excreta have their origin in these developing erythroid elements.[15]

The presence of hemolytic anemia in 3 such individuals has been studied using glycine labeled with isotopic nitrogen (N^{15}).[17–20] These data confirmed the increased rate of hemoglobin catabolism in these patients and further demonstrated that the nitrogen atom in glycine was the specific nitrogenous precursor for all three porphyrins—protoporphyrin, coproporphyrin, and uroporphyrin. Surgical removal of the spleen[14] was followed by an abrupt fall in the concentration of circulating plasma and erythrocyte porphyrin, while urinary and fecal excretion of uroporphyrin and coproporphyrin were reduced to very low levels and no evidence of excessive hemolysis remained. Coincident with this change, skin photosensitivity to sunlight disappeared. *Nevertheless, the abnormality in porphyrin metabolism remained,* although it was altered quantitatively.

In this instance, the metabolic error appeared to be primary in the erythroid elements of the bone marrow. An excessive demand for hemoglobin synthesis during hemolysis enhanced the requirement for protoporphyrin and was attended by formation and excretion of large amounts

Read at the Pediatric Grand Reunion honoring Dr. McQuarrie on his 25th year of service to the University of Minnesota.

of uroporphyrin and coproporphyrin. There is no biochemically proved explanation for this overproduction of type I porphyrin, particularly when all known heme compounds are formed from protoporphyrin which is type III. The role played by the spleen in controlling erythropoiesis in the marrow is equally mysterious. Finally, the factors placed in operation by circulating porphyrin which induce skin photosensitivity and hirsutism are unknown. Erythrodontia and pink discoloration of bone obtained at autopsy undoubtedly are due to deposition of porphyrin with calcium phosphate salts. In vitro studies have shown that calcium phosphate precipitates have a pronounced affinity for uroporphyrin.[21] These questions can be clearly stated and tested by experimentation now that the nature of this disorder has been clinically and chemically clarified and the site of the metabolic disturbance located.

2. *Porphyria hepatica.*[4,10,15,22] A pediatrician seldom must undertake the practical management of this form of porphyria, since its onset in practically all recorded cases occurs after adolescence. Nevertheless, the curious behavior of this interesting disease should be stressed with special emphasis on the clinical and chemical features which distinguish it from erythropoietic porphyria. Porphyria hepatica may be further divided into two clinical entities.

The *acute intermittent type* is more common in females and frequently runs a rapid course characterized by severe abdominal colic, psychic disorders, weakness, hypertension, constipation, oliguria, convulsions, and coma which is often fatal. The excreta contain excessive amounts of uroporphyrin and coproporphyrin zinc complex with type III isomers usually predominating over type I and high concentrations of the monopyrrole, porphobilinogen[23,24] are present especially during symptomatic periods. Bone marrow aspirates fail to show the characteristics observed in porphyria erythropoietica and there is no evidence of hemolysis. Biochemical studies of the liver show high concentrations of porphobilinogen, modest amounts of preformed porphyrin, and reduced catalase activity.[15,25]

The *cutanea tarda* variety of hepatic porphyria is less common and runs a more chronic course.[10,15,22] Skin photosensitivity, pigmentation, and serious evidence of hepatic dysfunction may be combined with any of the symptoms of acute intermittent porphyria. The urine is orange or reddish in color and porphobilinogen may, on occasion, be present. Both uroporphyrin and coproporphyrin are excreted in excess in urine and stool with type III the predominant isomer. The bone marrow is normal but liver biopsy shows huge amounts of preformed porphyrin with very little porphobilinogen.[15] Many of these patients ultimately develop cirrhosis of the liver and a survey of their records often reveals that they had been exposed to hepatotoxic agents.[22]

The multiplicity of clinical manifestations and chemical changes in hepatic porphyria has considerable attraction for the investigator, and laboratory study of this disease has rapidly advanced since the induction of experimental porphyria in rabbits and rats with Sedormid.[26,27] This experimental disorder closely resembles human hepatic porphyria, and much information has been gained about the structure and chemical nature of porphobilinogen as well as the behavior of the enzyme, liver catalase.[10,25] A pronounced reduction in liver catalase activity in both human and experimental porphyria has led to the suggestion that liver cells are the source of excessive porphyrin in the hepatic form of the disease, which probably results from their impaired ability to synthesize catalase.[10] The symptomatology and liver dysfunction have been found to be related to the inactivity of this enzyme.

Porphyria experimentally induced with Sedormid in the chick embryo impairs its growth and differentiation.[28] The significant growth lag which appears in the treated embryos a few days after injecting Sedormid into their yolk sacs persists for at least thirty days after hatching. Abnormalities of the embryo include shortening of the lower beak, clubbed down, malformation of the legs, weakness, and unsteadiness which resemble, in some respects, certain deficiencies of B vitamins. Evidence is accumulating which points to a defect in the metabolism of purine in experimental porphyria. Since the embryos are able to catabolize exogenous adenine in a normal fashion, the defect may be in the biosynthetic pathway.[29] When the vital role of purine in certain coenzymes and nucleic acids is considered, it is tempting to speculate upon the widespread changes which might follow reduced purine formation. For example, defective formation of the coenzyme flavin-adenine-dinucleotide might be expected to produce symptoms of riboflavin deficiency if the limiting component were *either* the vitamin or purine. This concept may be important, since some of the malformations in the Sedormid-treated chick embryo can be reproduced by riboflavin deficiency.[30] Other features relating purine synthesis to porphyrin formation will be considered in the following section.

PORPHYRINURIA AND THE BIOSYNTHESIS OF PORPHYRIN

The term porphyrinuria refers to excessive urinary excretion of any porphyrin. Porphyria is a term used when uroporphyrin is the urinary pigment. Protoporphyrinuria never appears in man, but coproporphyrinuria has been observed in such varied conditions as pernicious anemia, iron-deficiency anemia, cirrhosis of the liver, lead poisoning, poliomyelitis, infectious hepatitis, and rheumatic fever.[8,10]

Children with acute rheumatic fever studied during the past two years showed a highly significant increase in urinary coproporphyrin during the acute phase of the illness, which slowly returned to normal during convalescence.[31] Nontoxic oral doses of aspirin over long periods of time failed to affect the urinary porphyrin excretion. No evidence of significant changes in the erythrocyte porphyrin or bone marrow which might influence the porphyrinuria could be demonstrated. Coproporphyrin isolated from these patients was invariably nearly all type III isomer. An understanding of the mechanism of porphyrinuria in this disease may throw light on its pathogenesis. At present, there is little direct evidence to demonstrate that it is related to disturbed hemoglobin synthesis in the bone marrow.

During the past decade, the biosynthetic pathway by which porphyrin is formed has been carefully mapped.[32–34] Figure 1 illustrates the succinate-glycine cycle and its interrelationships. Thus, the amino acid, glycine, and one of the members of the tricarboxylic acid cycle, succinate, are joined to form ultimately delta-aminolevulinic acid which is then oxidatively deaminated to form alpha-ketoglutaraldehyde. The lat-

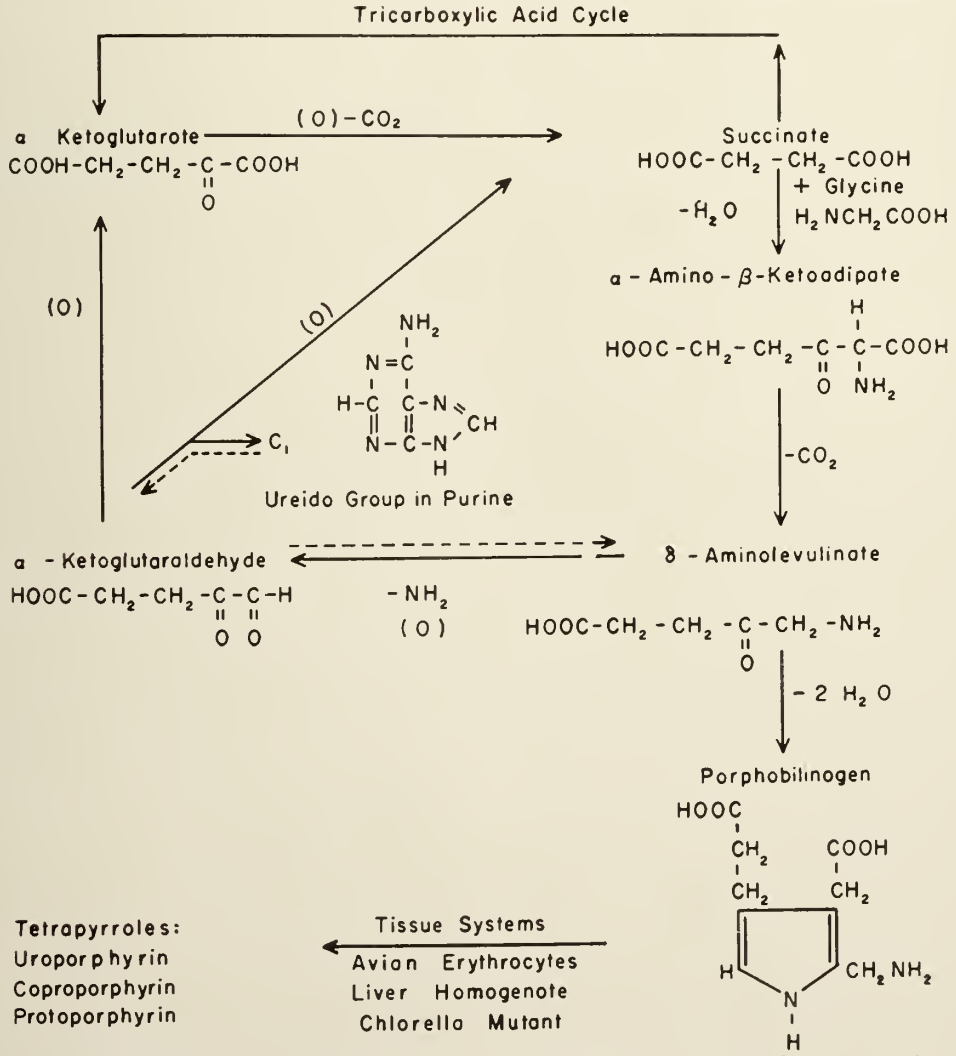

Fig. 1. Succinate-glycine cycle interrelations. (Redrawn from Shemin, D., and Russell, C. S.: J. Am. Chem. Soc. 75:4873, 1953.)

ter compound may either contribute a single carbon fragment to the biosynthesis of purine and re-enter the tricarboxylic acid cycle as succinate or simply be oxidized to alpha-ketoglutarate.[33] Delta-aminolevulinic acid is therefore a precursor of purine, as well as a highly active precursor of protoporphyrin. The latter step is presumably accomplished after condensation of two molecules of delta-aminolevulinic acid to form the monopyrrole, porphobilinogen. There is ample evidence that tissue systems can rapidly convert porphobilinogen to any one of three porphyrins.[35–37] Following this evidence that the biosynthesis of purine and porphyrin are related through a common precursor, it is tempting to speculate that increased porphobilinogen production in porphyria might result from a metabolic block at the point where delta-aminolevulinic acid undergoes oxidative deamination (figure 1). This would interfere with the formation of single carbon fragments impairing purine synthesis and also causing delta-aminolevulinic acid to accumulate under conditions favorable for its conversion to porphobilinogen and porphyrin. Since an inverse relationship between porphyrin formation and uric acid excretion has been demonstrated experimentally,[29] it is entirely possible that adverse effects on purine synthesis from a variety of causes might be reflected through increased porphyrin production. During the induction of experimental porphyria with Sedormid,[27] it has repeatedly been noted that coproporphyrinuria precedes the appearance of both uroporphyrin and porphobilinogen. This suggests that a mild manifestation of the metabolic error is coproporphyrinuria, but more severe degrees are marked by the appearance of porphobilinogen and uroporphyrin. This point is further strengthened by the fact that increases in urinary uroporphyrin have been observed in the coproporphyrinuria of lead poisoning.[10] This hypothesis should be added to others which seek to explain the mechanisms causing the metabolic alterations observed in coproporphyrinuria, hepatic porphyria, and Sedormid porphyria. Further studies of the relationship between purines and porphyrins in conditions characterized by porphyrinuria should continue to add to the extensive information already accumulated through clinical and biochemical research.

SUMMARY

Selected aspects of porphyrin metabolism in porphyria and porphyrinuria which are of interest to clinicians have been briefly reviewed. An additional hypothesis stemming from the biosynthetic relationship between porphyrin and purine is offered for the mechanism of hepatic porphyria, experimental porphyria, and coproporphyrinuria.

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(Continued on page 48A)

New Oral Sulfonamide Dosage Form with Prolonged Action

LE ROY J. STEPHENS, M.D., and
WILLIAM E. HENRICKSON, M.D.,
St. Louis and Poplar Bluff, Missouri

THE PAST FEW YEARS have seen a resurgence in the use of sulfonamides in chemotherapy of many infectious diseases. These drugs are dependable, quite uniformly effective in susceptible conditions, and economic. However, like all medication dependent upon uniform blood levels for optimum therapeutic benefits, the cooperation of the patient and of the nursing attendants is essential for faithful adherence to the prescribed dosage schedule. The fact that sulfonamides require, in serious illness, round-the-clock dosage at four- or six-hour intervals sometimes leads to unfaithfulness in adhering to a prescribed schedule[1] and often is a hardship on the patient because his rest is disturbed.

Therefore, it seemed important to us to investigate a new oral liquid dosage form of sulfonamides suspended in a fat emulsion vehicle designed to maintain therapeutic blood concentrations of the sulfonamides throughout a twenty-four-hour period upon twice-daily dosage at twelve-hour intervals. This development is based on earlier experimental observations which showed that the administration of certain sulfonamides in a menstruum of absorbable fat improves absorption of the drug into the bloodstream and enhances the chemotherapeutic effect over that obtained from administration of the drugs in aqueous vehicles.[2]

This communication presents a preliminary study of the absorption in experimental animals and in normal human subjects of sulfonamides from this new dosage form as compared to absorption from conventional forms. The administration of a sulfonamide in the oil emulsion vehicle is also compared for its therapeutic effect in an experimental infection in mice with the administration of the drug in an aqueous vehicle. Observations are reported on the therapeutic effect and adequacy of blood concentrations of sulfonamides that were achieved and maintained on a twice-daily dosage schedule of triple sulfas in an oral fat emulsion vehicle in a series of 54 patients.

LE ROY J. STEPHENS, *a 1936 graduate of St. Louis University School of Medicine, is assistant professor of clinical pediatrics at St. Louis University.* WILLIAM E. HENRICKSON, *a 1950 graduate of St. Louis University School of Medicine, is chief of pediatrics at Poplar Bluff Hospital, Poplar Bluff, Missouri.*

MATERIALS AND METHODS

The new dosage form of the triple sulfonamide was constituted as follows:

Sulfamethazine Sulfadiazine Sulfamerazine	Meth- Dia-Mer Sulfonamides	10 per cent (10 gm. per 100 cc.) or 2 per cent as indicated

Vegetable oil (highly emulsified)—50 per cent
Sucrose—12.5 per cent
Flavoring agents and preservatives—traces
Water, q.s.ad.—100 per cent

The new dosage form of the single sulfonamide was similar in composition except that sulfadiazine replaces the other sulfa drugs. The terms "aqueous" sulfadiazine or "aqueous" sulfonamides will be used to designate the drugs in an aqueous vehicle without the presence of oil or fat.

Absorption studies. Blood concentrations in 2 groups of mice, of 19 to 21 gm. in weight, were determined after oral administration of a single dose of 0.5 cc. (10 mg.) of aqueous sulfadiazine —2 per cent, and sulfadiazine in an oil emulsion vehicle—2 per cent, respectively. Dosage was by means of gavage and withdrawal of blood specimens by heart puncture at the time intervals shown in figure 1. The blood of 5 mice was pooled for each determination.

Experimental infection. The experimental infection in mice was produced with strain C203, *Streptococcus hemolyticus,* by inoculating mice intraperitoneally with 100 M.L.D. of an eighteen-hour virulent culture. This experimental infection has been previously used by various investigators[4] and, in our hands also, uniformly causes death in 100 per cent of control untreated mice within twenty-four to forty-eight hours after inoculation. The groups of mice were variously treated by stomach tube at intervals and dosage as indicated in table 1.

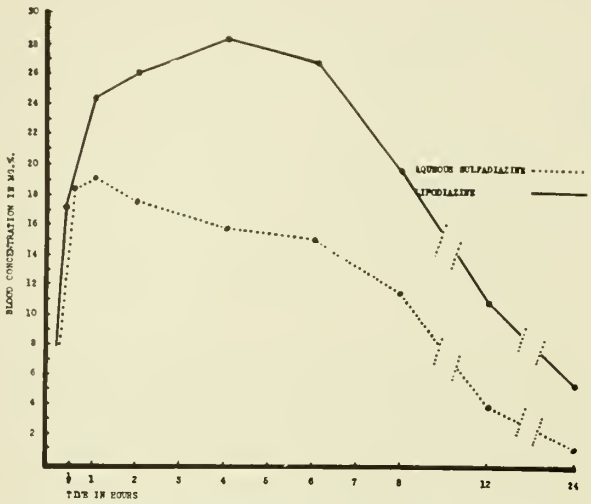

Fig. 1. Blood concentrations obtained in mice after single oral doses of sulfadiazine as Lipo-Diazine and in aqueous vehicle.

Single doses of sulfadiazine in the oral fat emulsion vehicle were given to 3 normal human subjects for the purpose of determining the absorption of sulfadiazine into the blood stream from the fat emulsion vehicle in comparison with absorption from an aqueous vehicle. Both dosage forms were tested in the same subjects at intervals of one week. Blood specimens were drawn at the intervals shown in figure 2 and were analyzed for sulfadiazine concentration by the method of Bratton and Marshall,[3] using a Klett-Summerson photoelectric colorimeter. This method was employed for all the blood concentration studies, and only the concentrations of free sulfonamides are recorded.

Clinical study. The clinical observations were made on patients hospitalized at the Poplar Bluff Hospital. Patients were of both sexes from 2 weeks to 57 years of age suffering from a variety of infectious conditions or requiring pre- and postsurgical prophylaxis of potentially septic conditions. Dosage of triple sulfonamides in an oil emulsion vehicle was administered orally on a twice-daily regimen and except for supportive measures this constituted the sole specific therapy.

RESULTS

Figure 1 shows the blood concentration time curves obtained in mice after ingestion of a single dose of 10 mg. (0.5 gm. per kilogram) of 2 per cent sulfadiazine in the oil emulsion vehicle as compared with the blood concentrations after equal doses of 2 per cent sulfadiazine in an aqueous vehicle. About equal levels appear up to the first hour, but, thereafter, sulfadiazine in an oil emulsion vehicle effects higher levels than aqueous sulfadiazine, and the higher concentrations are maintained through a twenty-four-hour period. At the twelve-hour interval there is still a therapeutic concentration of more than 10 mg. per 100 cc. with sulfadiazine in an oil emulsion vehicle while the aqueous sulfadiazine group manifest blood concentrations of 4 mg. per 100 cc.

Table 1 indicates that sulfadiazine in the oil emulsion vehicle is more protective against the experimental infection in mice than is aqueous sulfadiazine.

Comparative blood concentration time curves in human subjects corroborated the findings in the experimental animals. Figure 2 illustrates that on equal single doses of 60 mg. per kilogram (approximately ½ gr. per pound) of sulfadiazine in an oil emulsion vehicle results in a peak blood level of 8.3 mg. per 100 cc. as compared to 4 mg. per 100 cc. for aqueous sulfadiazine, both performed in the same subjects. The figure

TABLE 1
COMPARATIVE THERAPEUTIC EFFECT OF SULFADIAZINE AS LIPO-DIAZINE AND IN AQUEOUS VEHICLE IN HEMOLYTIC STREPTOCOCCAL INFECTIONS OF MICE

Dosage form of sulfadiazine	*Mg. sulfadiazine per dose*	*Number of mice*	*Number of mice dying on days following infection*						*Percentage surviving*			*Average survival time*	
			1	*2*	*3*	*4*	*5*	*6*	*3 days*	*7 days*	*14 days*	*Days*	*Per cent*
2 per cent sulfadiazine in 10 per cent acacia. Dose—0.5 cc.	10 mg. once daily 3 days	20		1		3	3	1	95	60	60	10.1	72.4
2 per cent sulfadiazine as Lipo-Diazine. Dose—0.5 cc.	10 mg. once daily 3 days	20							100	100	100	14.0	100
1 per cent sulfadiazine in 10 per cent acacia. Dose—0.5 cc.	5 mg. once daily 3 days	20	1	3	2	3	2	1	70	40	40	7.65	54.6
1 per cent sulfadiazine as Lipo-Diazine. Dose—0.5 cc.	5 mg. once daily 3 days	20							100	100	100	14.0	100
Controls— no medication		20	18	2					0	0	0	1.1	7.8

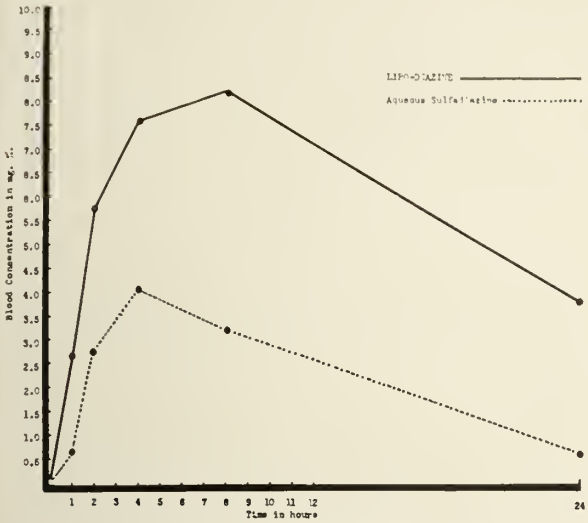

Fig. 2. Blood concentrations of sulfadiazine obtained in human subjects after single oral doses of sulfadiazine as Lipo-Diazine and in aqueous vehicle.

is a composite of results obtained in 3 subjects, each tested with both dosage forms of the drug.

Triple sulfas in an oil emulsion vehicle were administered to 53 patients both prophylactically and therapeutically for a variety of conditions. Response was uniformly favorable to a twice-daily dosage at twelve-hour intervals. Duration of dosage varied from three days to ten days depending upon the requirements of the condition and was well accepted.

The triple sulfas in an oil emulsion vehicle were administered routinely at 8 A.M. and 8 P.M., and blood specimens for sulfonamide determination were drawn on the first day at the eighth hour after dosage and thereafter just a few minutes prior to the administration of a subsequent dose. Thus, using the curve in figure 2 as representative, the values between 8

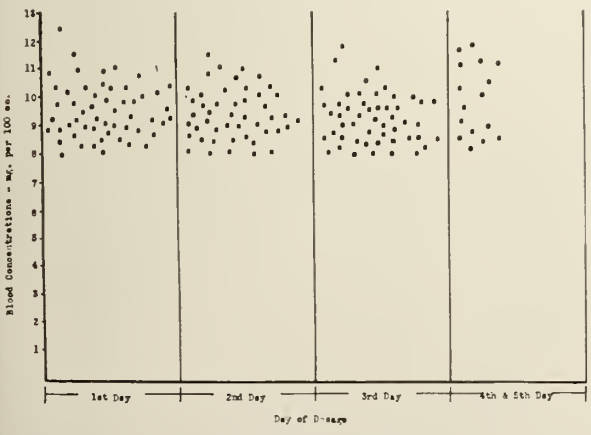

Fig. 3. Range of sulfonamide blood concentrations found in patients on a twice-daily dosage of Lipo-Triazine.

TABLE 2
DISTRIBUTION OF CASES

	Number of cases	
	Children	*Adults*
Lobar and bronchopneumonia	21	1
Acute bronchitis	6	1
Acute rheumatic fever	2	
Presurgical infection	4	1
Postsurgical prophylaxis	2	4
Pre- and postpartum infection		9
Septic sore throat—tonsillitis	1	
Scarlet fever	1	

and 12 mg. per 100 cc. shown in figure 3 represent the blood concentrations at their lowest ebb in the descending phase of the curve. The concentrations are expressed in terms of the total of free sulfadiazine, sulfamethazine, and sulfamerazine. The therapeutic response in this series was uniformly good. In 22 cases of bronchopneumonia and lobar pneumonia, patients responded fully as rapidly as compared with previous observations in patients treated with conventional dosage forms on four- or six-hour dosage frequencies. These patients became afebrile in twelve to twenty-four hours after initiation of dosage.

Triple sulfas in an oil emulsion vehicle were given to 9 patients with pre- and postpartum complications on the twice-daily schedule either as a prophylactic measure or for therapy of an existing sepsis upon admission. All responded promptly and favorably. Other cases in both children and adults, as listed in table 2, resulted in as rapid progress as might be expected from conventional dosage schedules. Toxic manifestations were not encountered in this small series of patients, most of whom received medication for less than five days.

The consistent maintenance of adequate blood concentrations of chemotherapeutic agents has long been established as a requisite for optimum therapeutic management. The need for continuing frequent dosages is often difficult to impress upon the patient, particularly after temperature and acute illness have subsided and the feeling of well-being has surpassed the less apparent and more gradual resolution of tissue pathology. In instances of prophylactic dosage too, particularly in children, an apathy often develops, if not outright unwillingness to maintain a consistent dosage schedule.

The emulsified fat in both the single and triple new dosage forms is reported to be in a minute particle state conducive to rapid utilization similar to the fat of oral fat emulsions that are now

recommended for maintaining adequate caloric intake during febrile and other illnesses.[5]

While this study was not directed toward attempting to explain the mode of action of simultaneously administered fat in enhancing sulfonamide absorption, it is of interest to find that other investigators, [6,7] had observed that higher blood concentrations of sulfonamides were attained in patients in whom dosage was administered after ingestion of food than in fasting subjects.

CONCLUSIONS

1. Sulfonamides in an oral fat emulsion vehicle are absorbed to higher and more prolonged blood levels in experimental animals and human subjects than sulfonamides absorbed from an aqueous vehicle.

2. Sulfadiazine in an oral fat emulsion vehicle gives comparatively better protection to mice experimentally infected with streptococci than does the drug in an aqueous vehicle.

3. Twice-daily dosage of triple sulfonamides in an oral fat emulsion vehicle resulted in sustained therapeutic blood levels with good clinical responses in a series of 53 patients.

4. It is felt that sulfadiazine in an oral fat emulsion vehicle and sulfadiazine, sulfamerazine, and sulfamethazine in an oral fat emulsion vehicle provide convenient means of adequate sulfonamide medication with reduced frequency of dosage.

The sulfadiazine in an oral fat emulsion vehicle (Lipo-Diazine), the sulfadiazine, sulfamerazine, sulfamethazine in an oral fat emulsion vehicle (Lipo-Triazine), and the other sulfonamide preparations used in this study were supplied through the courtesy of Donley-Evans & Co., St. Louis.

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Phthalamaquin may be used effectively for the control of bronchial asthma. The drug is a quinoline derivative that acts selectively on the respiratory tissues and the reticuloendothelial system. Charles F. Geschickter, M.D., of Georgetown University, Washington, D. C., reports that 80 per cent of 503 patients were benefited by therapy with the drug. Results were satisfactory in 86 per cent of the children, 80 per cent of elderly subjects, and 72 per cent of young adults. The usual dose is 50 mg. of the organic salt orally or intramuscularly or 200 to 500 mg. of the ascorbic acid form intravenously. With long-term therapy, the drug may be safely given orally in daily amounts of 3 mg. per kilogram of body weight.

Charles F. Geschickter: South M. J. 48:497-509, 1955.

Evaluating the Suicide Impulse in the University Setting

VIGGO W. JENSEN, M.D.
Detroit, Michigan

Suicide rates in the United States climb steadily upward from the age of 6 to a peak at about the age of 60, and then fall again. In 1951, the last year for which statistics are published, the number of suicides in the 45 to 55 age group, which has the highest incidence, was 3,306 compared with 940 in the 15 to 25 age group. This number of actual suicides in the younger age group gains significance from the fact that the occurrence of suicidal *gestures* is more common in young people from 15 to 25 years of age than in any other group. My experience has been that though not all people who experience suicide thoughts or impulses always make an attempt, the majority who are successful suicides in late middle age have made some sort of suicide gesture or expressed the impulse in their youth. Because of this fact it seems important to regard young persons who make suicide gestures as potential suicides of later life, and to direct as much effort as possible to preventing the youthful gesture from becoming a later fatality.

First, in our consideration of the suicide gesture in the university setting I would like to review briefly the general state of emotions in young people by quoting from Anna Freud's excellent description[1]: "Adolescents are excessively egoistic, regarding themselves as the center of the universe and the sole object of interest, and yet at no time in later life are they capable of so much self-sacrifice and devotion. They form the most passionate love relations, only to break them off as abruptly as they were begun. On the one hand they throw themselves enthusiastically into the life of the community and, on the other, they have an overpowering longing for solitude; they oscillate between blind submission to some self-chosen leader and defiant rebellion against any and every authority. They are selfish and materially minded and at the same time full of lofty idealism. They are ascetic, but will suddenly plunge into instinctual indulgence of the most primitive character. At times their behavior to other people is rough and inconsiderate, yet they themselves are extremely touchy. Their moods veer between light-hearted optimism and the blackest pessimism. At times they will work with indefatigable enthusiasm, and at other times they are sluggish and apathetic." This, then, is that human maelstrom, the adolescent and late adolescent, who is so often encountered in the university.

The following material is divided into two general sections: In the first section we will consider 11 typical problems pertinent to university life which may precipitate suicide gestures. In the second section we will consider again some of the characteristics of the young person in the context of their effect on his suicide impulses.

1. First in our list of typical problems is the separation from home, family, friends, and amours which can produce a deep sense of loss. Fortunately, this is usually seen in the form of harmless homesickness and, except in the most dependent of persons, it soon disappears as friends are made of students and teachers. Occasionally a student struggling with the initial phase of adjustment to a new situation feels overwhelmed by the vast number of new strangers, even as he felt overwhelmed by a new sibling early in life, and he possibly becomes suicidal. Or, if he was one of many children in the family, he may become depressed with a sensation of anonymity or depersonalization in a large university. However, rather than become significantly depressed, these students often drop out of school or transfer to another college, perhaps smaller, where they can feel less anonymous.

2. The student who attends college away from his parents frequently experiences a new freedom, which may lead him into his first sexual experience. This may be anticipated to produce in many students a great sense of guilt which can result in suicidal brooding as well as lesser

VIGGO W. JENSEN, *a 1946 graduate of the University of Michigan, is assistant professor of psychiatry at Wayne University Medical School and supervisor of the Mental Hygiene Clinic at the university.*

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symptoms such as anxiety, difficulty in concentrating, and so on. In our experience at Wayne University, this feeling of guilt is a common factor beneath the presenting complaints of female students especially, and more than one young lady who has presented herself as hopelessly suicidal has been cured when she was allowed to expiate her guilt by confession to an understanding counsellor and was given some advice and possibly insight.

Case report. Jo Ann, a 19-year-old sophomore, left her extremely dominating and frightening mother to live in the dormitory. Soon she became involved with a boy who was tender toward her and she had her first affair. She came to the Mental Hygiene Clinic in a severe depression with suicidal implications. She was given intensive treatment and for over a year the material of her treatment dealt continually with her guilt about her sexual transgression.

3. Another serious moment may result when an immature girl or boy becomes hopelessly infatuated with a student or instructor who, sooner, or later, rejects him. The rage which results may be incapable of expression and lead to the most varied of symptoms, for example, anxiety, insomnia, difficulty in concentrating, hypochondriac preoccupations, or depression, any one of which may be accompanied by self-destructive thoughts. Almost as a rule, we look first for a recent disappointment in love in the history of students appearing at the health service with such symptoms.

Case report. Ruby S. was seen by a health service physician at the request of her roommate who observed that she did not rouse from her sleep one morning. Suicide was implied as she had taken an unknown number of barbital tablets the night before. During the day on which she was examined, she awoke and finally revealed that the gesture was precipitated when she had a casual coffee date the night before with a boy toward whom she could not express a deep infatuation. His failure to recognize her feelings caused her to feel horribly rejected, whereupon she decided she had no course out of her hopeless frustration but to die. Fortunately her attempt was not serious and she recovered without incident.

4. A common problem is the bright student who achieved academic success in high school with relatively little difficulty. Such a student frequently expects to have the same success in college studies with the same small expenditure of effort. When he discovers either through low grades or actual failure that this is not possible, he experiences a severe injury to his pride which may result in suicidal feelings, with or without significant depression. The severity of the effect of such failures on the individual is usually dependent to a large degree on how much the failure was expected by him.

5. Another variation of the problem of narcissistic injuries is the beautiful girl whose primary aim is that of being loved and adored, her beauty being the means by which this is accomplished. Unfortunately for her, intellectual considerations are primary in grading examinations. She usually mistakes the academic failure as a failure in being lovable and may try to become a permanent sleeping beauty with an overdose of Seconal.

6. The "intellectual" student may do very well in college studies, but become gradually discouraged and depressed if he begins to suspect that his chronic disparagement of things erotic is really a rationalization for inner inhibitions. He is especially apt to face this situation if he becomes involved with a girl and loses her because she has tired of an entirely platonic or perhaps ascetic relationship. His intellect may fail him in such a situation and suicidal wishes overtake him.

7. Some young people regard the field of higher education as a field in which to make hay rather than one in which to acquire knowledge or information. Such a student may busy himself with developing his love life, always putting off until next semester the studying necessary to satisfy his parents or his own conscience. When he awakens from his amatory enterprises and discovers that finals are upon him, he may become terribly frightened and desperate and the love dream becomes an anxiety dream from which suicide may appear to him to be the only escape.

8. Familiar to all university personnel is the student who is studying toward his parents' goal rather than his own. Such a student may not be able to rebel against his parents' wishes and follow his own, but instead may become progressively more disturbed and depressed about his hopelessly submissive ways. A student in such a dilemma may view his suicide wishes with growing seriousness as an excellent way to freedom.

Case report. Dorothy B., a freshman, consulted a social worker in our Mental Hygiene Clinic shortly before freshman examinations because she felt trapped in her suicidal feelings. Her father was dead and she was attending the university at her mother's insistence. Her extreme passivity was apparent and she described her mother as viciously dominating. The severity of her dilemma became apparent later when she brought in a letter in which her mother threatened to kill her if she dared to leave school!! In her treatment she was allowed to express her feelings against her mother and her own ambitions became apparent for the first time in her life. She left school, found a job at which she did very well, and eight months later reported that she was happy at her new work and independence.

9. Varying degrees of anxiety before important examinations is normal and to be expected. Also, in the normal student, examination anxiety provides stimulus to succeed; but if this anxiety

reaches the proportions of paralyzing panic or assumes the form of crippling depression, suicidal intentions may be involved. An extreme example of this is illustrated in the following case:

Case report. Daniel H. had always had severe anxiety before and during examinations in high school, and had greatly feared his first freshman exams. In an attempt to master his fear he decided to take some intelligence and aptitude tests. During these tests he suddenly jumped up and ran screaming into the street. He jumped into a snowbank, telling a watching policeman that he was trying to put his fire out. During his stay in a psychiatric hospital he voiced numerous suicidal feelings until he recovered from his psychosis.

10. Anxiety about examinations usually appears in the context of the fear of failure—implicit in this, however, is the threat of success. Many students with a pronounced fear of failure continue in their efforts and are successful—indeed, they often appear to become successful because of the haunting fear of failure. The more insidious problem, in our experience, is the student who appears to have no such fear to spur him on to success and who develops slowly a loss of interest in his work, his goals, and his degree. Rather than developing anxiety, he develops an apathy, loss of interest, and even boredom. More often than not, toward the end of his college years, he usually tends to give up, wants to change his major field of study, or quit school and go to work—anything other than and short of his original intentions for graduation. Occasionally a depression develops with suicidal intentions apparent, which *usually is mistaken as the cause* of his failure rather than the result of it.

Generally, the dynamic problem is this: the successful acquisition of knowledge threatens to create anxiety, frequently manifested as a fear of failure; but this anxiety does not develop because, instead, an inhibition is developed. This inhibition is in the form of withdrawal from attempts to acquire knowledge and the goal of graduation, loss of interest, apathy, and boredom. The aggressive energy which has been stalemated by the inhibition leads to depressive feelings and possibly to suicidal impulses. With such a student, the outcome depends on many factors in his personality. Some are capable of continuing toward obtaining their degree after failing a few examinations. Others change their field of study to a field less emotionally threatening and obtain their degree. Probably a greater number give up without graduating, and, in our experience, the greatest number leave college in the early years. Those who have consulted our Mental Hygiene Clinic usually are in their third or final year and appear either because of depression with suicidal thoughts, or because they are alarmed by the development of an intractable and mysterious loss of interest which threatens the investment of time and energy they have made toward their degree. In such cases, where a true inhibition has developed, we have found that extensive psychotherapy has been necessary to overcome the inhibition.

11. The problem of the fear of success may appear in a somewhat paradoxical form in the student who continues to study for years, obtaining one degree after another. In such cases, there is an inhibition of the *use of* knowledge which may not appear as a problem for many years unless the individual does not have the academic talents or economic means to hide in the classroom until all the courses in the catalog are exhausted.

Now that I have mentioned some of the factors in the university setting which may precipitate gestures in those persons with suicide tendencies, I would like to enumerate some of the specific emotional factors in the young person which may precipitate his suicidal tendencies.

1. The tendency to *emotional lability* or mood swings which frequently can make emotional mountains today out of what will be molehills tomorrow, and thus create a life or suicide feeling about a matter prosaic to a more mature person.

2. An *impulsive tendency* which frequently leads to action where thought is more appropriate. When the problem of suicide tendencies is involved, this impulsive action can occasionally create a fatality although only a suicide gesture was intended.

3. The *instinctive pressure* which occurs in adolescent years normally creates a tremendous strain in the psychic system and, normally, the ego is busy managing this head of pressure. If the energy from the conflicts of childhood was never adequately managed, it may recur and increase the pressure occurring in adolescence to the breaking point. This situation may result in psychosis or suicide or in such tendencies.

4. Very important in any treatment situation with the adolescent is the relative *weakness of the defenses compared to the relative strength of the instincts.* This implies that all interpretations of unconscious material must be given sparingly and with great caution lest the reaction to the interpretation produces untoward results. For much the same reasons, treatment or counseling situations between student and therapist of opposite sexes should be handled with due regard for the urgent fantasies that may be provoked in the student.

These four characteristics, then, constitute a special risk for the young person with suicidal tendencies and create a special challenge to any therapist or counselor who deals with him. My comments will not be complete, however, until I mention some of the facets of the young person which give reason for optimism in the treatment of his suicide tendencies.

First, he is receptive and impressionable; ready to identify with anyone who appears strong to him; ready to accept aid from anyone who appears willing to give aid.

Next, his emotional energy is still free enough and flexible enough to form new behavior patterns. Frequently, all that is necessary is some education on a conscious level to broaden the emotional horizon and reveal different solutions to a seemingly hopeless problem.

Third, because the emotional energy in the young person is flexible, he usually has a great capacity for sublimation, and nowhere are the opportunities for sublimation greater than in a university setting. Opportunities for varied fields of study and for varied social activities are rapidly becoming limitless. The self-centered deposits of energy which occur in any suicidal problem can be redirected outward into dozens of possible channels.

A fourth consideration, of great value especially to those responsible for helping the young person, is the possibility of immense gratification from the results.

As I mentioned in the beginning, the person who commits suicide in late middle age has invariably made a gesture or expressed the impulse in his youth. Thus, to give a young person with suicidal impulses a new lease on life may prevent him from becoming a fatality statistic twenty years later.

REFERENCE

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Topectomy and medial and precoronal lobotomy are often effective for patients with pseudoneurotic schizophrenia who are not benefited by other therapy.

With precoronal lobotomy, all of the white fibers of the frontal lobes 2 cm. anterior to the coronal suture plane are cut. Only white fibers of the medial half of each frontal lobe in this area are severed by medial lobotomy.

Paul H. Hoch, M.D., J. Lawrence Pool, M.D., Joseph Ransohoff, M.D., James P. Cattell, M.D., and Harry H. Pennes, M.D., of the New York State Psychiatric Institute, New York City, report that of 37 patients investigated six to forty-eight months after surgery, 65 per cent were significantly improved. However, since 88 per cent of patients observed thirty-six to forty-eight months after treatment were improved, gains may continue for more than two and one-half to three years after the operation.

Patients benefited by psychosurgery are freed of anxiety and other symptoms that formerly paralyzed function and regain satisfaction from living. A patient may return to work, learn new skills, take academic courses, resolve domestic and social problems, or abandon dependency on parents. Depth of emotional feeling is not impaired, and the basic structure of the personality is not altered. Underlying stigma of schizophrenia is unchanged.

Onset of illness before age 15 is an unfavorable prognostic sign. Operative outcome is not correlated with age of the patient or duration of illness.

Paul H. Hoch, J. Lawrence Pool, Joseph Ransohoff, James P. Cattell, and Harry H. Pennes: Am. J. Psychiat. 3:653-658, 1955.

Immediate Care of the Automobile Accident Victim

MOORE MOORE, JR., M.D.
Memphis, Tennessee

THE FIRST PERSON to treat the victim of an automobile accident is usually not a specialist. This may be just as well, because the degree of severity of such injuries cannot be predicted at the time of the accident. By the same token, all specialists should remember that they are doctors first and specialists afterwards in any situation involving public, single, multiple, or mass injury.

So that emergency care may be effective, the physician must have ready a plan of action. This means that a rapid physical examination must be done first, since each victim must be presumed to have multiple injuries and adequate information cannot be gained any other way. This will include two aspects: (1) treatment of existing injuries, and (2) prevention of further injury, shock, and so forth, by improper care or handling. Thus the relative priority of treatment will be established.[1]

Absolute top priority goes to proof of an intact airway, since no more than three or four minutes without O_2 can pass without danger of permanent cerebral damage from anoxia. If there are no breathing movements and the heart is still beating, artificial respiration must be started at once (chest pressure – arm lift method) and continued to a definite conclusion. Later, O_2 can be given endotracheally.

An unobstructed airway may be provided by the face-down position, tongue traction or elevation, oral airway, or tracheotomy (especially in the unconscious patient). Asphyxia is especially prevalent in mandible, neck, or maxillary injuries in unconscious patients and may be caused also by pneumothorax, flail chest, cardiac tamponade, or hemothorax. Sucking wounds of the chest must be sealed immediately. Flail chest must be stabilized by compression bandage, towel clip on rib, and so on.

MOORE MOORE, JR., *a 1933 graduate of the University of Tennessee Medical School, is attending orthopedic surgeon at Methodist and St. Joseph's hospitals and consultant at the United States Naval Hospital, all in Memphis.*

Second priority goes to stopping hemorrhage. Bleeding from exposed and accessible areas is obvious and can usually be controlled by local continued pressure over as wide an area as possible. Tourniquets are usually to be avoided because most are applied incorrectly and merely increase venous bleeding while failing to stop arterial hemorrhage.[2] Permanent thrombosis may result from a tourniquet left on too long.

However, after the need for a tourniquet is established, it should be left in place until blood replacement has begun and the patient has reached a place where definitive care of the arterial injury can be done. Application should be over a broad area and probably not below the knee or elbow, where it is of little use.

Open wounds must be treated only by covering them with a sterile or clean dressing. Shock is usually caused by hemorrhage, soft tissue damage, and burns. Shock may be defined briefly as a disproportion between the circulating blood volume and the vascular tree. One theory, which is not proved, postulates a vasopressor factor (VEM) from the kidney and a vasodilator factor (VDM) from the liver as well as the spleen and skeletal muscle to some extent, both being normally in equilibrium. In shock which becomes irreversible, the one overcomes the other with resultant pooling of tremendous quantities of blood in the splanchnic capillary system. This is thought to be caused by inability of the liver to detoxify the vasopressor factor present in the hypotensive and anoxic state which leads to irreversibility if it persists. In anoxic states, renal circulation becomes negligible and, thus, little or no VEM is synthesized to balance the VDM. The general consensus of opinion is that ultimate collapse of the organism is the result of peripheral circulatory failure. Among the factors thought involved are: (1) fluid loss, (2) neurogenic influences, (3) changes in capillary permeability, and (4) toxic and humoral agents.

Hemorrhage may be visible or invisible – the former is rarely missed as an aid to diagnosis or treatment. The latter may be in the extremities, chest, abdomen, bladder, kidneys, and so

forth. In addition, multiple contusions, abrasions, and lacerations may be present. Adjunctive measures in the exsanguinated patient may be lifesaving. Some can be done almost instantly, such as the head down position, while definitive measures are being provided. Merely raising the foot of a litter 18 in. has been observed to raise arterial blood pressure 20 points. A blanket should be placed both under and over the patient as warmth is important.

One special infrequent hazard of motor vehicle accidents deserves separate mention – the very real possibility of permanent cataract formation from contact with battery acids. Only prompt copious washing with water can prevent or ameliorate this condition.

Only after these primary potential lethal alterations in body physiology are controlled, or well in the process of control, should the patient be transported. In moving him, special attention should be paid to the maintenance of the mutual anatomic relationships of skull and spine. If spinal injury is suspected because of local tenderness and pain on palpation, help should be secured so that the victim may be moved by 2 or 3 persons, preferably with manual traction on the head and possibly in the prone position. It is always better to await adequate transport facilities than to be overcome by sympathy and further injure the victim by doubling him into the back of another automobile. Long-bone fractures should be splinted wherever the patient is lying.[3] British and American World War I records show that use of the Thomas' splint *alone* reduced the mortality of compound femoral fractures by 25 per cent. However, splints need not be complicated or unwieldy – almost any moderately rigid material will suffice, such as a magazine, newspaper, pillow, small tree, or branch. The arm may be bound to the torso. Padding of some sort is desirable. Splinting at the scene of the accident will prevent compoundings and reduce shock and fluid loss in the tissues.[4,5]

Overdosage with morphine is still a recurrent problem even today – and probably happens most often because information concerning previous dosage is usually not known.

The amount of fluid which may be lost in the tissues from the circulation is not to be underestimated. For example, in a closed fracture of the femur with an average length thigh measuring 16 in. in circumference at its mid-point before injury and which swells so that its average cricumference is increased by 2 in., the amount of fluid lost in the thigh has been calculated to be as much as 2,200 cc. Both bones of the lower leg fracture with associated heavy swelling may add up to 1,300 cc. Considering that persons with multiple skeletal injuries also usually have many abrasions, contusions, and lacerations from which both whole blood and extracellular fluid are lost, the total depletion may go to 4,000 or 5,000 cc., which is about 35 per cent of the extracellular fluid of a man weighing 70 kilograms. Also, one must not overlook the very real possibility of perforate or blunt abdominal injury in which large amounts of plasma are lost into the gut. Blood counts a few days after injury are usually quite revealing, in spite of what may be thought to be adequate replacement therapy.

The repair solutions are whole blood, plasma, plasma expanders, and fluids and electrolytes in proper concentration. While whole blood is being readied, the others should be used. The best of these is dextran, which is now being used in preference to plasma in the armed forces. It is equally as good as a resuscitative agent and obviates the risk of homologous serum jaundice prevalent with pooled blood plasma. Electrolytes in proper concentration are best supplied by one-sixth molar lactate-Ringer's solution, as normal saline provides fluid of wrong electrolyte concentration.

Whole blood ranks above all measures in resuscitation from severe hemorrhage. World War II and Korean experience have shown that universal donor blood may be used without individual crossmatching without fear of reaction. In Korea, it was demonstrated that the basic fundamental factor which determined the need for large transfusions was the presence or absence of large areas of muscle injury. (Each femur was given 2 pints automatically.) The excess loss of blood in muscle wounds is easily understood when one considers the great amount of muscle which may be damaged by implements of war, industry, or traffic. The same relative condition holds true in closed or open extremity civilian wounds, more so when no splinting has been done and when improper handling takes place. This does not take into account the real possibility of concomitant major vessel or nerve injury in such situations.

Auxiliary examinations such as x-ray films of the skull or extremities, before control of the primary death producing conditions of asphyxia, hemorrhage, and shock, are contraindicated by obvious but too frequently not remembered reasons.

I would like to emphasize again that the first person to treat or see an accident victim may in large measure determine the final result in terms of both mortality and morbidity. Thus,

(Continued on page 48A)

Lancet CLINICAL REVIEWS

This department of THE JOURNAL-LANCET *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Problem of Pulmonary Fibrosis

R. DREW MILLER, M.D.

Rochester, Minnesota

THE PROBLEM of diffuse pulmonary fibrosis has become more challenging to the practicing physician in recent years. One reason for this has been the increasing knowledge of a variety of agents or processes which may produce the clinical picture of pulmonary fibrosis, with progressive dyspnea and roentgenographic evidence of diffuse, bilateral pulmonary shadows. Despite the increased number of diagnostic tools and the increased understanding of the disturbed pulmonary function, an etiologic diagnosis is often difficult to establish. From a practical standpoint, the extent to which diagnostic procedures are carried out depends on the patient's disability and whether the process appears to be progressing or static.

CASE REPORT

A 39-year-old priest of German extraction registered at the Mayo Clinic on February 23, 1953, complaining of progressive exertional dyspnea and pain in numerous joints, especially the knees and ankles.

In 1944, while serving in the United States Army in the South Pacific, he noted the gradual onset of dyspnea. His battalion surgeon noted that the patient had clubbed fingers. In 1946, transient pain in the knees and ankles appeared after the patient returned to a colder climate. Results of routine chest roentgenograms when the patient left the service were interpreted as negative. History revealed no previous exposure to unusual dusts, industrial or otherwise. No previous illness suggested a pneumonic process. He smoked a half to one package of cigarettes daily, and he had a slight cough productive of a scanty clear or yellow sputum. Climbing one flight of stairs caused pronounced dyspnea, but he could walk several blocks slowly on level ground. Since 1946 he had noted some swelling and aching in the ankles and knees, which became more troublesome in wet, cold weather. The symptoms in the joints had become more troublesome during the two years prior to his registration at the clinic.

This patient was well developed. Dyspnea developed during moderate exertion. There was pronounced clubbing of all fingers and toes (figure 1). A few flat, small lymph nodes were palpable in the left supraclavicular space. Scattered, dry crackling rales were noted over the entire fields of the lungs. Chest expansion was 1 in. Diffuse bilateral pulmonary shadows were evident in roentgenograms (figure 2). Roentgenograms of both ankles showed periosteal thickening compatible with pulmonary osteoarthropathy involving the lower third portions of both tibias and fibulas. Bones of the hands and wrists were not changed except for enlargement of the tufts of the distal phalanges.

Studies of pulmonary function showed the vital capacity to be 60 per cent, and the maximum breathing capacity 100 per cent of normal. The residual volume per total capacity ratio was 39 per cent. The 7-minute alveolar concentration of nitrogen (concentration of an end-expiration sample of gas after the patient had breathed 100 per cent oxygen for 7 minutes) was 1.8 per cent, normal $<$ 2.5 per cent. Arterial oxygen saturation was slightly reduced at rest, 93.7 per cent, and a decrease to 85 per cent occurred after 1.4 minutes of exercise, demonstrating impaired diffusion of oxygen across the alveolar-capillary membrane. The patient exercised for 3.6 minutes while breathing 100 per cent oxygen. The arterial oxygen saturation was 100 per cent during the entire period in which the patient exercised, essentially ruling out a "right-to-left" cardiovascular shunt.

Results of routine urinalysis were normal. The value for hemoglobin was 15.2 gm. per 100 cc. of whole blood. The erythrocyte count per cubic mm. was 5,430,000, and the leukocyte count, 9,700. A differential leukocyte count gave normal results. The cell volume (hematocrit) was 53 per cent. The volume of whole blood was 89 cc. per kilogram of body weight. Results of a test with second-

R. DREW MILLER, *a 1946 graduate of Northwestern University Medical School, is with the section of medicine at the Mayo Clinic, Rochester.*

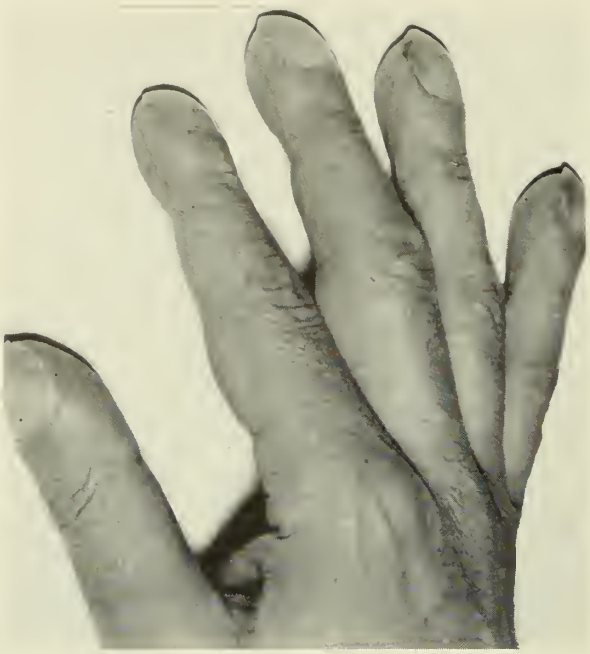

Fig. 1. Clubbing of the fingers of a 39-year-old male whose condition was diagnosed as diffuse pulmonary fibrosis with pulmonary osteoarthropathy.

strength tuberculin were positive; but histoplasmin and coccidioidin skin tests were negative.

An electrocardiogram showed evidence of right ventricular hypertrophy. In lead V_1, a relatively tall R wave was accompanied by a deeply inverted T wave. In leads V_2 and V_3, the T waves were sharply diphasic. Phlebotomy was done, and 400 cc. of whole blood was removed without any definite improvement. Biopsy of the lymph nodes in the left supraclavicular region revealed nonspecific inflammatory changes. Bronchoscopic examination disclosed nothing abnormal.

A specimen for biopsy of the lower lobe of the right lung was obtained subsequently through an intercostal incision in an attempt to determine an exact nature of the pulmonary fibrosis. The pathologic report was "diffuse parenchymal fibrosis." The terminal air passages contained collections of histiocytes and giant cells. No granulomatous inflammation was found in the interstitial tissue.

Bacteriologic study of the sputum, bronchial washings, and surgical specimens of lymph node and lung revealed no tubercle bacilli, fungi, or Brucella organisms.

After the negative results of bacteriologic studies on the surgical specimens, a program of cortisone therapy was initiated because of progressive exertional dyspnea. The daily amount was 200 mg. of cortisone administered orally in 4 equally divided doses, and this was continued two weeks. Next, 150 mg. of the agent was given in 3 divided doses daily for one week. During the fourth week the dose was reduced to 25 mg. administered four times daily.

Studies of pulmonary function at the end of one month showed no objective change. Exercise tolerance increased very little, although the patient felt somewhat stimulated by the fairly large dose of cortisone. The pain in the joints associated with pulmonary osteoarthropathy disappeared entirely during the period of steroid therapy. The use of cortisone was gradually reduced to a maintenance dose of 50 mg. daily in 4 equally divided doses, and continued for six months. During the sixth month of therapy the dose was gradually reduced and finally stopped.

Studies of pulmonary function showed no further reduction in the various values. In fact, the measured tolerance of exercise in the laboratory showed an increase of 2.1 minutes while the patient was breathing room air, and the arterial oxygen saturation decreased only to 87 per cent after this period of exercise. After the administration of cortisone was stopped, he experienced only occasional slight pain in the ankles during very cold weather, and this pain was easily controlled with aspirin. At the time of this report, eighteen months had elapsed since the first dose of cortisone was given, and no pronounced progression of exertional dyspnea had occurred. It was difficult, however, for the patient to continue his responsibilities to a busy parish, and he was limited to part-time duties.

COMMENT

Efforts in this case to isolate a specific causative factor, occupational pneumoconiosis, "collagen" disease, microbial infection, or lipid aspiration were unsuccessful, even when direct studies were made on the involved pulmonary tissue. Histologic features did not suggest sarcoidosis, either in the lymph node or in the pulmonary tissue. Studies of pulmonary function demonstrated the classic pattern of pulmonary fibrosis with replacement of lung volume (decreased vital capacity and total capacity) by the pathologic process without impairment of air flow (normal maximum breathing capacity). The pronounced fall in arterial oxygen saturation with exercise indicated a marked impairment of diffusion of gases across the alveolocapillary membrane, sometimes referred to as the "alveolocapillary

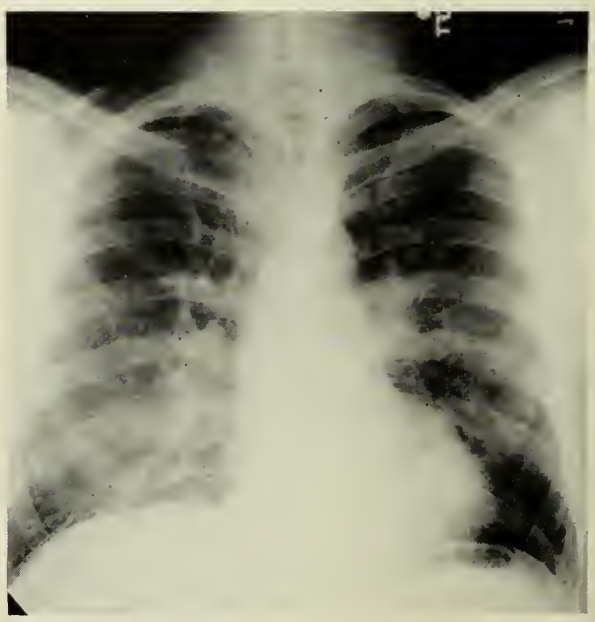

Fig. 2. Diffuse bilateral pulmonary shadows characteristic of diffuse pulmonary fibrosis.

block." The histopathologic evidence correlated well with the physiologic findings.

Biopsy of the lung is occasionally the only method of demonstrating organisms or specific tissue changes leading to diagnosis and treatment. Culture of the tissue for various types of organisms is essential in making a diagnosis, and occasionally special tissue stains for fungi or fat droplets are of equal value. Chemical analysis is helpful, especially if berylliosis is suspected.

When all possible studies have failed to reveal the etiologic factor, a diagnosis of diffuse "idiopathic" interstitial pulmonary fibrosis or Hamman-Rich syndrome may be made. Although Hamman and Rich described a syndrome in which progressive disability developed over a period of months, the diagnosis they described has been made in cases in which the course was more chronic. As knowledge of new etiologic agents becomes apparent, fewer patients will have the conditions now qualified as "idiopathic." Recently, one of the hypotensive agents, hexamethonium, when used in large doses, has been found to be associated with pulmonary changes resembling those described by Hamman and Rich.[1,2] Reversal of the abnormal bilateral pulmonary shadows and exertional dyspnea occurred in some cases after administration of the drug had been discontinued.

The appearance of clubbed fingers and also symptomatic pulmonary osteoarthropathy of the knees and ankles is a somewhat unusual feature in our case. Clubbed fingers frequently are associated with cyanotic congenital heart disease, with bronchiectasis, and also with localized intrathoracic neoplasms. Pulmonary osteoarthropathy, clinically resembling rheumatoid arthritis and radiographically showing periosteal proliferation of the "long bones" (radius, ulna, tibia, and fibula) also has been described as a frequent complication of intrathoracic neoplasms and occasionally of bronchiectasis.[3,4] The mechanism of periarticular and periosteal changes is not known. That such changes may complicate diffuse "idiopathic" pulmonary fibrosis is demonstrated in this case. Also of interest to note is the fact that the pain of osteoarthropathy disappeared after the use of steroid hormone therapy, and did not recur to a significant degree even after the dose of cortisone was gradually reduced and finally was discontinued.

Finally, the management of diffuse pulmonary fibrosis poses a profound problem.[5] If a specific agent is found which responds to a definitive program, there may be reason for some degree of optimism, even though the changes are by no means completely reversible. If all possible diagnostic procedures have ruled out the known etiologic agents to the satisfaction of the clinician, he is then faced with the decision of whether or not to institute nonspecific hormone therapy. Cortisone is notoriously variable in its symptomatic effect on patients who have fibrosis of the lung, including sarcoidosis.[6] Even after temporary symptomatic improvement, removal of the drug may be followed by pronounced exacerbation of dyspnea, so that the patient becomes "dependent" on the hormone. Occasional precipitous deaths have been attributed to withdrawal of the drug.[7] The deleterious effect of cortisone on patients with tuberculosis is widely appreciated. The problem of retention of sodium as a result of cortisone therapy in patients with cor pulmonale is also ever present. Nevertheless, when confronted with a severely dyspneic patient who has progressive symptoms, institution of a program of cortisone or ACTH therapy should be seriously considered, since an occasional patient appears to be significantly and sometimes dramatically improved thereby.

ADDENDUM

Since this manuscript was submitted, several patients with severe progressive pulmonary fibrosis have been treated with prednisone (Meticorten). They achieved varying degrees of benefit similar to those obtained by patients receiving cortisone. Freedom from aggravation of salt and water retention was a distinct advantage in the use of prednisone. This newer drug was tolerated by one patient even though pronounced peripheral edema developed while he was receiving cortisone.

Meticorten furnished by Schering Corporation, Bloomfield, New Jersey.

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Notes from a Medical Journey

Entebbe, Uganda, East Africa

Dear Jay:

Since last I wrote I got home from Switzerland, entirely recovered from the 'flu and determined to do six months' work in three so as to get off on the present job with urgent reports and papers written, research data analyzed up-to-date (what a hope!), lectures given at Ames and New York, and all in readiness for the work in South Africa and in Italy. As you can imagine, we took off on this trip more than a little red-eyed from lack of sleep. The South African Council on Scientific Research had invited me to Cape Town where we could at last get on with studying the Bantu, the Cape Coloured and Europeans in collaboration with our good friend Dr. J. F. Brock, professor of medicine.

So here we are, en route, exactly on the equator at Entebbe. Lake Victoria is sparkling in the sun a couple of hundred yards away. From the formal flower beds just outside the window, immaculate lawns sweep down to the water, only occasionally broken by great and strange trees. The Bougainvillea, tumbling down the wall and over the pergola in great masses of crimson, and the hibiscus grown into a 12-ft. hedge by the tennis courts, remind us of Mexico and of La Jolla, California, where our son is presently staying with my parents. That is until one of the big hibiscus flowers flies away. We rub our eyes but we were right the first time; it is a hedge of hibiscus in bloom and one of the flowers was a matching red bird. But the bird is no brighter than the dresses of the native Baganda women here who go swinging along with elegant carriage, their dresses sweeping to the ground in every imaginable color combination of rare harmony and brilliance glowing against their dark faces. The deep green hues of the tropical forest and the rich red of the earth makes a wonderful foil. Usually they are carrying something on their heads, anything from a huge basket of vegetables to a single bar of soap. This is a beautiful and peaceful land, with none of the strife of the Mau Mau not far away in Kenya or the fanatic nationalism of Apartheid of South Africa.

We have been staying a few days with Dr. and Mrs. J. N. P. Davies, professor of pathology at Makerere Medical College, at Kampala, 20 miles from here. Makerere is considered the best medical school in Central Africa and obviously maintains high standards with their small class (next

year they will increase to 20 admissions) of all colors of students who graduate with a University of London degree. "Jack" Davies has been the prime mover in bringing to light the prevalence of endomyocardial fibrosis among the natives here and in a vast region to the south. At home we think this condition is one of the greatest of rarities, but here it accounts for about 20 per cent of all the cardiacs. Yesterday I spent hours going over a hundred or so of the recent hearts from deaths from all causes (they get a very high proportion of posts), as well as a batch of saved-up specials and peculiars. The fibrosis was often the only lesion in the cases of death from heart failure, and this condition also appeared in a good many hearts of patients who never showed a sign of heart disease during life. There were cases where most of the ventricle was filled with a great white fibrous mass and frequently the fibres, apparently proceeding along the trabeculae, had produced valvular incompetence, particularly of the mitral valve. The aortic valve is never involved. Clinically, the picture corresponds to the mechanical situation and, therefore, suggests a rheumatic heart or, sometimes, constrictive pericarditis except in those cases where there is nothing evident but unexplained heart failure. No one knows the cause, but the commonest guess is that it is related to nutrition.

Of course I am here because of my ideas about the diet and the development of atherosclerosis. There is no doubt that the diet of the natives here is very low in fats (as well as in animal proteins) and that coronary atherosclerosis is extremely rare, though renal disease and hypertension are not. It is a startling experience to work down a long table covered six deep with adult hearts, most of which have at least a good part of the aorta attached, and see so little of the common picture at home. The insides of the aortas of men in the 50's and 60's often are like a good grade of grey glove leather (in other words like our children!), instead of the patchy, yellow spotted and lumpy stuff that you and I probably have to offer. I spotted one of the Minnesota Grade 3 and Dr. Davies said, "Probably a butcher." Actually, it proved to be a case of nephronephritis aged 50, but later I did find that the local butchers, who naturally have a fair consumption of the leavings of their trade, contribute a substantial proportion of Minnesota-type arteries.

Yesterday I talked with the surgeons who said they have lots of thrombo-embolic complications after surgery in the local Europeans and then they proceeded to count on their fingers the cases among the Baganda they have seen in the past few years. This reminds me of the wartime experience in Norway where postsurgery thrombo-embolic complications decreased even more abruptly than coronaries when the diet fat consumption dropped. It is not possible to put the blame on semistarvation because, though obesity is rare, so is emaciation and general undernutrition.

The diet of the local natives would horrify the nutritionists at home, and it certainly is low in meats and dairy products but it is generally adequate in calories and the classical stigmata of nutritional deficiency are not common among adults. The worst situation is that of the babies at weaning and up to the age of 5 or 6. From breast milk the change is to the adult diet, watered down a bit -- gruel or porridge of cereals containing low-quality proteins, bananas, sweet potatoes, cassava,

tapioca, or manioc and little, if any, milk or dairy products or meats. The result is an appalling frequency of "kwashiorkor" which seems to be mainly, if not entirely, the result of a deficiency of high-quality proteins. The babies often exhibit various types of dermatitis and tend to have down-like hair deficient in pigment so that their heads are covered with a soft reddish or grayish fuzz. More constant, however, is the edema, diarrhea, apathy, and irritability. The liver is big and full of fat, proteins in the blood plasma are very low as is the blood cholesterol. They are usually not emaciated and postmortem seldom reveals much indication of general undernutrition. If not too far gone, they respond well to skimmed milk and dry skim milk powder would save thousands of babies a year if it were available.

To me, perhaps the most significant thing about the recent research on kwashiorkor is the finding that when good proteins are fed the fatty livers rapidly lose their fat and at the same time the blood cholesterol rises greatly, though neither cholesterol nor fat is being fed. This ties in with everything else we know about cholesterol and fat metabolism. Whenever fat has to be transported from one place to another in the body, or mobilized to be combusted, there must be a proportionate amount of cholesterol to form the lipoprotein complex in which the fat is transported. The fat itself, like the cholesterol itself,is not soluble in the blood plasma or any of the rest of the aqueous system of the body, so the water-soluble lipoprotein complex must be formed. The infant with kwashiorkor gets rid of his fatty liver when he has a sufficient supply of protein to make the lipoprotein and, hence, the cholesterol in the blood rises greatly at this stage of high fat transport. When we Americans eat a diet with a high content of fat, we almost always seem to have plenty of the protein to form the lipoproteins needed to carry the fat in the blood and so the cholesterol rises in the blood. The liver almost always can synthesize all the cholesterol wanted for the lipoprotein and so all is well. The one danger is that some of the large concentration of lipoprotein may get "stuck" in the intima arteries and so leave a deposit of cholesterol there to produce atherosclerosis and coronary heart disease.

Doesn't this idea seem to fit all of the facts? We can even see why physical exercise should be beneficial because, first, it speeds up the circulation and so prevents the sluggish condition where deposition is favored, and, second, the increased energy metabolism tends to burn up the excess fat as it becomes available in the blood. This is all greatly simplified, of course, but even in detail it makes good biochemical sense.

But now the tropical night is coming on with a rush and we leave early tomorrow for the nine-hour flight to Victoria Falls and Johannesburg.

With all the best to you, the "U" and all in Minnesota,

As ever,

Ancel Keys

Section on PAIN

Comments concerning this Section, criticisms, or suggestions for papers will be most welcome. Physicians are cordially invited to submit articles pertaining to pain for consideration. All inquiries and manuscripts should be sent to Dr. John S. Lundy, 102 Second Avenue Southwest, Rochester, Minnesota, or to the Editorial Department, THE JOURNAL-LANCET, *84 South Tenth Street, Minneapolis, Minnesota.*

Herniated Cervical Disk and Atypical Facial Neuralgia

Muscle Spasm as a Pain Factor

BERNARD D. JUDOVICH, M.D., and
GOLDA R. NOBEL, M.D.
Philadelphia, Pennsylvania

HEADACHE and atypical facial neuralgia are frequent complaints in association with a herniated cervical disk or other painful lesions of the cervical spine. In the recent past, several investigators have discussed this problem, describing the syndrome and the possible pathways of pain transmission. Although many basic features of the headache are described alike, presumptive mechanisms of the headache have differed. This paper is a further effort to cast light upon the signs and symptoms and possibly the nature of this clinical picture.

Summarized briefly, two possibilities have been suggested to explain the mechanism of the pain projection from the cervical spine to the head and face. One involves irritation of the descending or spinal root of the trigeminal nerve with transmission of pain to the head and face, and the other pertains to pain which is sympathetic, caused by reflex stimulation.

From observations and facts reported by others,[1–4] as well as those of our own,[5–7] and attempting to correlate these findings, we hope that some part of this problem may be clarified.

We have been able to uncover but a single case in the literature which offers authentic objective evidence of a herniated cervical disk which produced irritation of the descending or spinal root of the trigeminal nerve. This case, reported by Elvidge and Li,[8] involved a midline herniated cervical disk at C4 and C5 interspace which presented signs and symptoms of an intraspinal space-taking or degenerative lesion. In addition, corneal sensitivity and corneal reflexes were absent. A circular area of anesthesia to touch, pain, heat, and cold, about 3 to 5 cm. in diameter in each cheek, was present. A similar area of anesthesia involved the anterior one-third to one-half of the trigeminal area of the tongue. The motor component of the trigeminal nerve was intact bilaterally. The patient did not complain of headache or facial pain. Laminectomy and removal of portions of the disk were followed by return of the corneal reflexes and return of sensibility in the face and tongue on the second postoperative day. This case presents definite objective findings which implicate the trigeminal nerve, and suggests a caudal limit of the trigeminal spinal sensory root hitherto not clinically demonstrable.

Raney and Raney,[1] in a comprehensive report on headache in association with herniated cervical disks, made observations which are identical with those found by the writers, especially the reproduction of radiating pain to the temporal, orbital, and facial regions by digital

BERNARD D. JUDOVICH, *a 1930 graduate of Hahnemann Medical College, is associate in neurology at the Graduate School of Medicine, University of Pennsylvania.* GOLDA R. NOBEL, *a 1931 graduate of Women's Medical College of Pennsylvania, is also at the University of Pennsylvania.*

pressure in the occiput. In connection with this type of headache, these investigators offer most important information, in that head pain due to a pathologic cervical disk is not relieved by section of the root of the trigeminal nerve nor by tractotomy nor by both, even when the pain is confined within the zone made anesthetic or analgesic.

Implicating the same pathway, Skillern[2] recently reported 100 cases in which pain was referred to the face or head, the mechanism of which, Skillern deduces, is by way of the descending or sensory root of the trigeminal nerve, as a reflex pain having its origin through C2 and C3 level from a painful greater occipital nerve. The tender point described in the occiput is identical to that described by Raney and to that previously described by the writers, both as to location and areas of radiation. Although Skillern does not directly associate this syndrome with herniated cervical disk, he does state that 16 per cent of the patients suffered with stiffness of the neck.

The facts which seem to be in agreement are: (1) that occipital pain, headache, and facial pain may exist alone or in conjunction with signs which involve the cervical spine; (2) that a tender point in the occiput is frequently found, and that stimulating this area may cause local pain or produce radiating pain to the temple, orbit, or face; and (3) that local anesthesia of this tender occipital point may abolish the headache.

Our opinion, which is based upon data presented in this paper, is that the headache in these patients is vascular in origin, the findings being identical to those observed in tension headache and other forms of vascular headache. In patients who are predisposed to tension headache, irritation of nerve roots or other painful somatic structures of the cervical spine appears to be capable of initiating reflex stimulation of the sympathetics, so that vascular headache may be precipitated. With the onset of pain in the cervical spine, the vascular headache often becomes a prominent and persistent feature of complaint. In the majority of our patients with signs of herniated cervical disk and headache, history revealed that the patient had suffered tension headaches off and on for years prior to the onset of cervical pain. In these patients, the cervical pain appears to act as a trigger mechanism in the production of tension headache in some susceptible individuals.

The fact that emotional stress can cause tissue changes is well known. It may precipitate headache by causing changes in the arterial circulation; it may cause development of a gastric or duodenal ulcer; and it may even precipitate a coronary attack. Probably emotional disturbances or tension situations release unknown stress substances which can produce the tissue changes resulting in psychosomatic manifestations.

The vertebral artery with its branches to each spinal nerve, the gray communicating rami from the sympathetics which join the spinal nerves for vasomotor supply to somatic areas and their hook-up to the various cervical ganglia, especially the superior cervical sympathetic ganglia which enters into the formation of plexuses about the internal and external carotids for distribution to the sympathetics of the head, all offer possible pathways by which stimuli could precipitate vasomotor irritability.

Jackson,[3,4] also, has emphasized the part played by the sympathetic distribution in the production of pain.

Skillern has theorized that the origin of the pain is in the greater occipital nerve and, by reflex radiation, stimulates the sensory branch of the trigeminal nerve. Facts which are contrary to this theory are: (1) the report by Raney that tractotomy in this type of headache does not abolish the pain; (2) the report by Skillern that 29 per cent of his patients suffered with bilateral symptoms. (From clinical experience, simultaneous bilateral involvement of identical nerves with reflex bilateral symmetrical pain reference would appear most unusual. This type of pain reference, however, is common with referred visceral pain and is especially true in vascular headaches); and (3) Skillern's report of the phenomenon of muscle spasm associated with the reflex radiation via the sensory root of the fifth nerve.

It is important to note that the occipital tender area described is a constant point—it is in a nondeviating location and marks an anatomic point. This fact has been reported by most observers. One should keep in mind that this point marks not only the location of the occipital nerve but also that of the accompanying occipital artery.

The following symptoms and signs are characteristic of this type of headache.

SYMPTOMS

The chief complaint is that of pain in the occipital and/or parietal, frontal, and temporal regions. The scalp may be sore when hair is combed and brushed. Facial pain or a sensation

of numbness or tingling in the cheek may occur. Pain may be unilateral or bilateral. A common symptom is a sense of painful pressure behind the eyeball on the affected side. Many patients complain of blurred vision. Discomfort may be felt in the ear in the form of fullness, pressure, or pain. The pain may radiate to the neck or shoulder. In some patients, occipital pain is either absent or minor, with the major discomfort ocurring in the temporal and orbital regions. In others, the maximum pain is occipital with little discomfort in the frontal or temporal region. At times a sensation of a tight band around the head is present. Throbbing pain is a frequent complaint. These are symptoms common to migraine, tension headache, histamine cephalgia, posttraumatic headache, and vascular headache in general. Symptoms may last for hours or days.

SIGNS

Although location of pain may vary and characteristic painful areas are not always present, an acutely tender point is usually found in the occiput, approximately midway between the tip of the mastoid and the midcervical spine, on the painful side if unilateral and on both sides if a bilateral headache is present. Deep pressure and rolling the tissues with the finger tip to cause irritation at this point frequently cause reference of pain to the ear, face, orbit, frontal, or temporal region, reproducing pain in the areas of complaint. Firm, sustained pressure may ease the radiating pain to the temple, orbit, or face. In addition to the tenderness in the occiput, tenderness is found over the superficial temporal and carotid arteries. The carotid tenderness is often, but not always, present. In seeking the presence of tenderness over the superficial temporal artery, pressure in itself may not make this sign apparent. Sharp tapping over the artery, however, usually causes a pronounced reaction of sensitivity as compared to the nonaffected side or other control areas. Tightening of the neck muscles may also accompany the headache; the latter occurs especially when associated with a lesion of the cervical spine.

Both the occipital nerve and occipital artery are located at this tender point. Radiation to the temple, orbit, and face is far beyond the distribution of the occipital nerve, and, since the occipital trigeminal reflex appears to be untenable, arterial pain remains as another possibility. When we consider that the superficial temporal artery and carotid artery are simultaneously tender with the occiput, and that injecting the occipital tender point with an anesthetic can abolish the temporal, orbital, and facial pain, then we may reasonably consider a vascular basis for this pain.

This technic of injecting the occiput has been applied not only in headache associated with herniated disk, but in tension headache and occasional cases of migraine. In all these groups, the sensitivity of the occiput and arteries were alike.

When occipital pain and/or tenderness is present, search should be made in other arterial regions for tenderness to establish evidence of vascular sensitivity. It is of interest to note that the act of rubbing and irritating the sensitive superficial temporal or carotid arteries does not produce radiating pain as is the case when the tender occiput is so stimulated.

It was observed on several occasions that when orbital pain was associated with temporal pain, anesthetizing the superficial temporal artery eased the temple pain but did not modify the accompanying orbital pain. Occipital infiltration, however, frequently abolishes the orbital pain within a few minutes.

TECHNIC OF INJECTION

A point midway between the mastoid tip and midcervical spine is palpated for a maximum point of tenderness. The area is marked with ink. Palpation is repeated to confirm the most acute point of tenderness. The area is shaved, a procaine skin wheal raised, and 3 cc. of 2 per cent procaine infiltrated until bone is contacted. This area should be palpated after the infiltration to be sure that all local tenderness has disappeared. If tenderness completely disappears and the headache persists, repeated infiltration usually is of no benefit.

Infiltrating this area with procaine very often causes complete disappearance of pain within a few minutes. This type of headache is differentiated from occipital neuralgia by pain reference to the frontal, temporal, orbital, facial, and shoulder regions and by the tenderness of the arterial distribution. In occipital neuralgia, pain and tenderness are limited to the distribution of occipital nerve.

When pain subsides because of occipital infiltration, it does so immediately. The duration of relief is unpredictable. Relief may last for hours, days, or months or may fail. So many patients obtain prolonged relief that the method appears to be of definite value in pain control.

THE CERVICAL SPINE

Patients with headache should have the cervical spine routinely examined to eliminate this structure as an etiologic factor. The cervical spine is examined for limited motion or "painful catch" by moving the spine through the full range of rotation, flexion, and extension, compression of the spine by pressure upon the head, and by noting response to traction, 35 to 40 lb.

Areas of radiating pain and elicitation of sensory and/or motor abnormalities help to localize the involved pain level. If downward compression of the cervical spine intensifies and reproduces the radiating pain, probably the cause is vertebral rather than extravertebral. Test traction frequently stops the pain for the duration of the pull. Patients with limited painful movement of the cervical spine, increased pain on compression, and relief by traction usually have a "mechanical cervical spine," very often a herniated intervertebral disk.

The following are examples of the many typical headaches we have observed.

CASE REPORTS

A 38-year-old male complained of severe left-sided brachial plexus pain for two months. The signs and symptoms were typical of a herniated cervical disk. Relief of the brachial plexus pain was obtained by using 45 lb. of motorized intermittent cervical traction and by infiltration of the left anterior scalene muscle with procaine. In addition, he had had an almost constant sensation of bilateral pressure in the occiput, associated with pain in both temporal regions and a feeling of eyeball pressure, with a sensation of burning and "sandy feeling" in the eyes. History revealed tension headaches had occurred for years prior to the onset of the cervical symptoms. Pressure upon the tender occiput eased the pain; rubbing reproduced some of the pain. On the initial visit, a bilateral occipital infiltration was done with procaine. Within a few minutes, the headache and eyeball pressure on both sides had completely disappeared. The abnormal sensation in the eyes completely disappeared. The patient had no headache for three days and then experienced a mild recurrence, but not in the eyes. The injections were repeated and the patient had relief for about a month. Benadryl, 50 mg. at bedtime, was prescribed. Relief lasted several months and the injection was again repeated.

G. C., a 41-year-old female, was taking treatment for brachial plexus pain after a whip-lash injury to the cervical spine. Objective findings were characteristic of a herniated cervical disk at C6 and C7 level. Pain was acute, with pronounced limitation of the cervical spine in extension or in attempting to rotate the chin to the right. Compression of the cervical spine by pressure upon the head caused radiating pain to the right second and third fingers. Head-halter traction at 40 lb. produced almost complete relief. The right triceps reflex was absent. Roentgen studies revealed narrowing at C5 and C6 and C6 and C7 interspaces. Excruciating pain developed in the right occiput six weeks after starting therapy, with pain referred to the right temple and eyeball. Pain intensity was such that the patient screamed and cried without control. An acute, tender point in the right occiput, midway between the tip of the mastoid and midspinous line was located. Pressure eased the pain; rubbing the tender spot increased the pain. The right superficial temporal artery was acutely tender to percussion, the left was not. The right carotid artery was tender as compared to the left.

The occipital tender point was infiltrated with 2 cc. of 2 per cent procaine. In two to three minutes the pain stopped completely and has not recurred for over a year. There was no history of headache prior to this time.

The following case history of atypical facial "neuralgia," although not associated with a lesion of the cervical spine, presents the typical vascular signs found with tension headache and is not recognizably different from the headache findings associated with a herniated cervical disk.

I. H., whose chief complaint was severe facial pain was referred with a diagnosis of tic douloureux. However, the characteristic signs of this condition were not present. The pain was constant instead of paroxysmal, without peripheral projection, and remained confined to the proximal half of the left mandibular region. Pain was not precipitated or aggravated by chewing or talking.

Examination revealed pronounced tenderness over the left occiput and the left superficial temporal and left carotid arteries. Rolling the tissues with deep pressure over the tender area in the occiput caused radiating pain to the lower jaw. Questioning brought forth the fact that there was a sense of pressure behind the eyeball. The patient had been under unusual stress as a supervisor of salesgirls during a busy holiday season.

The facial pain disappeared within three minutes after the tender area of the occiput was infiltrated with procaine. Benadryl, 50 mg. at bedtime, was prescribed. The patient stated a year later that the pain had not recurred. Diagnosis was atypical facial "neuralgia"—tension headache, vascular in origin.

I. M. had a chief complaint of headache and pain in the right shoulder girdle. The onset followed trauma, at which time patient was dazed and complained of head and neck pain. Roentgen studies of the cervical spine and skull at the time of the injury were negative. Patient later became hysterical and depressed. After psychiatric care, the depression and hysteria disappeared. The headache and shoulder girdle pain remained. The complaint of headache was associated with a constant full feeling which became acute at times. This pain was associated with a feeling of tightness in the occiput, sometimes referred to the ear, sometimes the whole head felt like a tight band and a tight pressure sensation involved the right eyeball. Headaches were worse in the evening and lying in certain positions increased the pain. Examination revealed the following: Motion was moderately limited when the chin was turned to the right shoulder. If an attempt was made to force it beyond this limit, sharp pain in the right lower cervical spine occurred. Rotating the chin to the left did not cause pain. Tilting the head to the right and pressing downward with the examiner's body weight caused sharp pain in the right lower cervical spine. Hyperextension of the cervical spine

was negative. Hyperflexion caused a mild pulling sensation in the right scapular region. No evidence of a scalene syndrome was found. Acute tenderness was present in the occiput midway between the tip of the mastoid and midcervical spine. Right superficial temporal artery was quite tender when compared with the left. Patient exhibited a reaction of pronounced sensitivity when finger percussion approached the artery. The left side similarly examined was negative. The common carotid artery was tender, the left was not. Infiltration of the tender point in the occiput with 2 cc. of 1 per cent procaine caused the entire headache and orbital pain to disappear within five minutes. The examination with reference to the head and neck appeared to be otherwise negative. Intermittent motorized traction at 35 lb. greatly relieved the pain and increased movement of the cervical spine.

M. D., a 42-year-old female, complained of a severe headache of four days' duration. The onset was sudden. History revealed tension headaches off and on for years, with increasingly severe headaches during the past year due to a situation of domestic strife. The headache at this time was extremely severe, associated with occipital pain and sharp pain in and behind the ear and intense pressure pain behind the eyeballs. Although the pain was bilateral, the acute pain was left sided. Aspirin, other analgesics, and barbiturates gave very little relief.

Examination revealed acute tenderness in the occiput and over the superficial temporal and carotid arteries. A placebo tablet was given to the patient with instructions to allow it to dissolve under the tongue. At the end of one-half hour, no relief was obtained. An identically appearing tablet of Hydergine was placed under the patient's tongue. In fifteen minutes the pain eased and in twenty minutes most of the headache disappeared. The patient was given another tablet at this time. A half-hour later the headache had completely disappeared and had not returned two hours later. The left occiput was infiltrated with 2 cc. of 1 per cent procaine, and the patient was instructed to take no drug other than 2 Hydergine tablets if headache recurred.

The next day the patient reported that no medication was necessary as the headache had not recurred. Late that morning, a tightness and throbbing was experienced in the back of the neck. Complete relief of pain was obtained in about fifteen minutes with 2 tablets of Hydergine. Relief lasted four hours. The next dose gave complete relief for five hours. Sleep was not interrupted for the next two nights. Continued use of Hydergine brought about eight hour periods of relief. Relief periods of three and five days followed. At the last report, no headache had been experienced for over a week, the first such interval in a year. The patient stated that Hydergine gave more rapid, more complete, and longer lasting relief of headache than any other medication she had taken.

This case is cited because it may cast some light upon the nature of the headache. Vasoconstriction and possibly edema appear to play a definite part in the pain mechanism. This is also suggested by the fact that a small amount, 2 cc., of procaine infiltrated about the occipital artery in many instances provides relief of pain within a few minutes.

B. S. complained of severe headache involving the occiput, the temples, and eyeballs; vertigo; pain and stiffness of the cervical spine; pain in the left shoulder girdle and arm; and pain in the low back and iliac crest for a duration of four months after injury with a prolonged period of unconsciousness.

The fifth cervical spinous process was tender to pressure. Extension of the cervical spine was limited and painful. Turning the chin to the left caused pain in the cervical spine. Compression of the left anterior scalene muscle caused pain to be referred to the left arm and mid-chest. The right side was not sensitive. Tilting of the head to the left and compressing the cervical spine downward caused pain in the left shoulder and chest. In addition to these maneuvers, it was noted that heavy traction of 35 to 40 lb. produced immediate cessation of pain. The left radial pulse was absent with a pronounced decrease in oscillometric readings of the left brachial artery as compared to the right, which was due apparently to a traumatic subclavian thrombosis. Neurologic examination was negative.

An acutely tender point was present midway between the tip of the mastoid and the midline of the cervical spine. Rubbing this area caused reference of pain to the temple. Sharp percussion with the finger revealed tenderness of the superficial temporal arteries and over the carotid. Motorized intermittent traction of 35 lb. to the cervical spine provided pronounced relief of the pain in the cervical spine. Hydergine abolished the headache in about twenty minutes. On one occasion when 2 Hydergine tablets were taken, transitory vertigo and diplopia developed. This did not recur with repeated doses. The patient obtained complete relief of headache and the Hydergine was discontinued. Headache did not recur over a three-month period.

N. R. complained of pain in the head and neck. Onset occurred December 19, 1953 after an automobile accident in which he injured his neck. He was dazed and as far as can be determined from the history may have been unconscious for a short period of time. This pain was localized to the cervical spine and the occiput, and was referred ot the temple and eyeball, more severe on the left side.

Examination of the neck revealed tenderness over the mid- and upper cervical spine. Tenderness was present in the occiput on both sides at points midway between the tip of the mastoid process and midcervical spine. The left side was acutely tender, but the right side was not nearly as tender. Rubbing the area on the left occiput caused radiating pain to the temple and eye. The left superficial temporal artery was acutely tender to finger tapping when compared to the right. On poking, the left carotid artery was much more sensitive than the right. Tilt of the head and neck to the left in compressing the cervical spine downward caused pain in the upper cervical spine. Rotation to either side caused pain in the upper cervical spine. Flexion was normal. The deep tendon reflexes were normal. The patient felt immediate relief of cervical pain with traction of about 30 lb. The findings were otherwise negative. The patient states that prior to the time of the accident he never suffered headaches of any kind.

On one occasion, during a headache attack, a wet pad was placed on the left lateral and posterior cervical region and one upon the parietal region of the head. A sine wave current caused spasm of the muscles in this region. The current was increased to maximum tolerance. This produced visible muscle contraction which was maintained for a twenty-minute period. The purpose of this procedure was to find out whether muscle

spasm in the upper cervical spine and scalp would produce headache in a susceptible patient.

At the end of twenty minutes the patient stated that the headache had decreased. This patient eventually obtained sustained relief after a period of motorized intermittent traction plus the use of Hydergine. The occiput was not infiltrated until his final visit in order to evaluate the action of Hydergine.

J. S. had a chief complaint of pain in the upper cervical region for a duration of approximately ten years. The patient feels that this pain was aggravated after an injury incurred when he dove into a pool containing only 2 ft. of water. He was told he had arthritis of the cervical spine.

Pain was constant, usually not excruciating, but occasionally became severe. Traction with 8 lb. of weight had been applied, and sleep was difficult without some form of sedation. In addition to the pain in the cervical spine, he developed a headache which caused pain in the right eye with blurring of vision. A recent complete eye examination was normal.

Rotation of the cervical spine to the left was limited. Hyperextension was normal. Rotation to the right was normal. Flexion was only slightly restricted and painful. This pain was always worse on arising in the morning and subsided with continued movement. The reflexes were normal. Pain occurred on compression of the cervical spine downward, especially with tilt to the left. An acutely tender area was found in the right occiput.

This, in addition to the orbital discomfort plus tenderness of the right superficial temporal artery and right carotid artery, indicated that this pain was possibly vascular in origin. Examination was otherwise negative.

The right occiput was infiltrated, and within a few minutes a definite but incomplete easing of the head pain occurred. The patient was given heavy traction, 30 to 35 lb. The left anterior scalene muscle was injected and the patient was given microwave therapy over the upper cervical spine. A placebo gave no relief of headache. Hydergine provided complete relief of his headache in a half-hour. The patient reported two months later that regular use of this drug abolished the headache almost entirely. Most days required the use of 2 tablets, but there were periods of two and three days in which no medication was necessary. Manual traction at home with 35 lb. produced almost complete relief of the neck discomfort.

MUSCLE SPASM

The concept that muscle spasm causes pain and that when it exists in conjunction with or is precipitated by an accompanying lesion it may cause additional pain, thus producing a vicious pain cycle, appears to be fallacious in certain respects. When we consider the individual aspects of muscle spasm in specific clinical conditions, a modified viewpoint is gathered. If we divide muscle spasm into two groups, the first in which an intrinsic or direct muscle disturbance is present, and the other in which the muscle spasm or disturbance is reflex in nature, differences in these two groups can be observed. Trauma, strain, hemorrhage, metabolic disturbance of muscle, inflammation, tender nodules, or new growths, of course, are intrinsic muscle disturbances and are a direct cause of local muscle spasm and pain. These constitute the group with intrinsic disturbance. In the second group, the muscle spasm is reflex due to irritation of pain sensitive structures in which no actual change takes place in the muscle other than spasm.

For example, the most common type of headache, tension headache, is claimed to be due, at least in part, to spasm of the neck and scalp muscles. In herniated cervical and lumbar disks and other mechanical disturbances of the spine, muscle spasm is said to contribute additional pain. In many forms of trauma, reflex spasm of muscles other than those actually injured may take place. Does this type of spasm cause pain?

In some basal ganglia disturbances, such as parkinsonism, tonic muscle contraction may take place. In psychosomatic disturbances and tics, tonic spasm with rotation of the head and neck is not rare. These patients do not complain of pain but of a tightness or pulling sensation instead.

In several patients who were particularly susceptible to tension headache, spasm of the muscles in the upper cervical spine and scalp was induced by electrical current and maintained for a period of twenty minutes. This was done while the patients complained of headache. In spite of the fact that spasm was greater in degree than that usually observed during tension headache, no symptoms were produced. While a larger series of patients might be more convincing, we were able to note that muscle spasm alone in these few cases did not produce headache.

In many cases of herniated disk, both in the cervical and lumbar regions, muscle spasm is frequently bilateral and commonly contralateral. In spite of the fact that the muscles on the side opposite the lesion may be almost board-like in their splinting action, usually these muscles are not tender or painful.

The concept that constant mild cervical traction is necessary to overcome muscle spasm for relief of pain is questionable. The bulk of evidence points to the fact that spasm which is associated with a "mechanical" painful neck, such as a herniated cervical disk, is reflex in nature and does not of itself cause pain. Symptoms are due to compression of the nerve root or other pain-sensitive structures, so that the resultant effect is a sensory-motor or motor-motor reflex which results in spasticity of the muscles supplied by the particular nerve root involved.

The reasons for this opinion are as follows:

When a herniated cervical disk is present and the paraspinal muscles are spastic with a loss of lordosis, compressing the cervical spine by applying strong pressure downward upon the head shortens the muscle but increases the pain. Tilting the head laterally to the painful side and pressing downward should relax or shorten the muscles on the painful side. Instead of relief, the radiating pain is sharply increased because of the compressive factors which are the actual cause of pain.

In approximately 40 to 50 per cent of herniated cervical disks, if a traction force of 30 to 45 lb. is applied, pain is instantly relieved either completely or partially the moment the force is applied and returns as soon as the force is released. Theoretically, if a muscle is spastic and painful, a sudden pulling force upon this muscle should produce increased pain and spasticity. However, the reverse occurs; the pain either stops completely or partially, which is further evidence that the muscle itself is not producing pain and does not add to the pain cycle. In acute torticollis due to intrinsic muscle irritation, traction causes severe pain.

In addition, many patients who had been hospitalized and treated by conventional light weight constant traction without relief obtained immediate or pronounced relief as soon as test traction with heavy force was applied. When this relief took place, it did so in a matter of one or two seconds, too soon to say that painful muscle spasm was overcome.

Brachial plexus pain is frequently blamed upon a "postural defect." Spasm, loss of lordosis, limited motion, and other postural changes associated with acute pain involving the cervical spine are usually due to lesions which involve the cervical spine and should not be blamed upon a "postural defect." The "postural defects" which are present appear to be due to reflex spasm.

The use of constant traction for herniated cervical disks and other mechanical lesions of the spine in which traction is indicated is of value only in a limited number of patients. Good results appear to be due to bed rest and immobilization and not to stretch force upon the spine. Many patients leave the hospital with their original pain and remain intractable to all methods of conservative therapy. In view of the fact that test traction shows that the average intractable case of brachial plexus pain is relieved with approximately 30 to 40 lb., it is difficult to conceive how 5 or 6 lb. can provide relief of pain in this particular group. An average of 6 lb. is required to overcome the surface traction resistance of head and cervical spine before any actual stretch can begin to take place upon the cervical spine structures.

Weight of head and neck at C6 and C7 level averages 11 lb. Surface traction resistance of this segment averages 6 lb. or more. Conventional traction of 5 to 6 lb. of hanging weight, therefore, applies no stretch to the cervical spine at this level.—Scientific Exhibit, A.M.A., Atlantic City, June 1955. In publication.

When a muscle such as the scalenus anticus is involved, it is true that muscle spasm in this instance causes added pain, but this is due solely to the fact that this particular muscle is strategically located so that it compresses the subclavian artery and components of the brachial plexus, and pain here is not due to intrinsic muscle irritation.

CONSERVATIVE TREATMENT

The most effective form of conservative therapy for a herniated cervical disk is heavy traction, usually in the 30 to 35 lb. range, at times more.[5–7,9] Motorized intermittent traction may be administered as an office or hospital procedure, or hand traction may be applied at home utilizing a head-halter, scale, and pulleys. With motorized intermittent traction nearly all patients obtained satisfactory relief of pain. This observation has been confirmed by others.[4,9]

If reflex scalene spasm appears to be causing pain, it is usually controlled by 1.5 to 2 cc. of 2 per cent procaine solution injected into the anterior scalene muscle.

Headache in association with painful cervical spine lesions, if not relieved by traction and ordinary analgesics, should have the occiput injected, providing that the criteria for this type of headache are established.

Hydergine, a new cranial vasodilator, seems to be of value in relieving headache associated with painful mechanical lesions of the cervical spine. Hydergine was administered in a limited number of patients with headache and herniated disk and in tension headache alone. Placebo tablets were given to 30 patients while they were complaining of headache. Prompt relief occurred in 9 patients and these patients were eliminated from the group as unsatisfactory subjects. Hydergine tablets to be dissolved under the tongue were given to 21 patients who failed to obtain relief with the placebo. Of these, 10 patients obtained relief of pain, 11 did not. The majority of patients had been taking analgesics ranging from aspirin to Demerol.

Relief of pain with Hydergine was obtained in fifteen to thirty minutes. Those patients who obtained relief were chronic headache sufferers who not only failed to be affected by placebos but obtained unsatisfactory relief with analgesics. In this group, 3 patients suffered with concussion headache as well as injury to the cervical spine. The fact may or may not be of significance that these patients obtained the most dramatic and satisfactory relief of pain of all the patients tested. All 3 had pronounced signs of vascular sensitivity, with occipital and orbital pain as outstanding symptoms.

The use of a supporting collar is indicated when pain in the cervical spine and roots is so severe that slight movements or the weight of the head or jarring causes acute pain.

Spinal studies are indicated in patients exhibiting signs and symptoms of a possible space-taking lesion who remain untractable to conservative methods.

COMMENT

A number of factors point to the likelihood that in the majority of instances the headache which is associated with painful mechanical lesions of the cervical spine is vascular in nature. These are as follows:

1. A tender point in the occiput marks the location of the occipital artery and nerve. Irritating this spot often reproduces radiation of pain to the scalp, frontal, temporal, and orbital regions. No nerve or other anatomic structure can produce this radiation except a blood vessel. The occipital nerve reflex by way of the spinal root of the trigeminal nerve at C2 and C3 appears to be untenable because tractotomy in this type of headache does not relieve the pain.

2. The frequent bilateral symmetric distribution of pain, often throbbing in nature, points to vascular rather than nerve involvement. It would be most unusual, not to say highly improbable, to find symmetric bilateral nerve lesions, with bilateral reflex radiation to identical areas, occurring with regular frequency. Since this type of bilateral headache is usually associated with a single laterally displaced disk, nerve transmission is less apt to be responsible.

3. In nearly all instances of these headaches, the occipital tender point was accompanied by tenderness of the superficial temporal artery and in most instances the carotid artery.

4. The frequent rapid disappearance of persistent severe headache, including temporal and orbital pain after injection of 1.5 to 2 cc. of 2 per cent procaine solution in the region of the occipital nerve and artery. This injection did not produce anesthesia of painful areas except at the point of local infiltration. A small amount of anesthetic at this point did not eliminate muscle spasm in the neck and scalp if it were a primary source of pain, nor did it account for the area relieved of pain by anesthesia of the occipital nerve.

5. Relief of headache in a significant number of controlled patients with the use of Hydergine, a vasodilator, and the frequent rapid relief with the small amount of procaine suggest a vasoconstrictive mechanism.

SUMMARY

Clinical observations suggest that the headache and atypical facial pain which are associated with a herniated disk and other mechanical lesions of the cervical spine appear to be, in most instances, vascular in nature.

These headaches present the same symptoms and objective findings as those encountered in tension headache. Cervical and scalp muscle spasm alone as a factor in the production of this type of headache and also in tension headache, does not, in this preliminary report, appear to play an important role.

The above findings may explain the reported good results in headache which are obtained by traction.

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Masked Sinusitis

CHARLES B. PORTER, M.D.
Grand Forks, North Dakota

THE GENERAL PRACTITIONER probably looks upon the treatment of acute nasal sinusitis as something of a nuisance. Sinusitis is quite common, especially during the season of upper respiratory infections. The patient feels miserable but he is likely to get well slowly and completely. No entirely satisfactory or rapid treatment is known, especially in the case of male patients who are not inclined to rest in bed. Also, women with several small children are reluctant to remain at strict bed rest for several days.

Fortunately for the physician, most cases of sinusitis do not result in serious complications. Severe maxillary or sphenoid sinusitis may cause pronounced symptoms, but only in cases of gross neglect is such sinusitis likely to endanger life. However, the frontal sinuses and sometimes the frontal cells of the ethmoid sinuses are so constructed anatomically that catastrophic illness may result.

The frontal sinuses are located between the outer and inner tables of the frontal bone. The anterior walls of the frontal sinuses are usually quite thick and contain marrow. Unfortunately, the posterior walls of the frontal sinuses are thin layers of compact bone behind which lies the dura covering the frontal lobes of the brain. The thin, posterior walls of the frontal sinuses are perforated by numerous vessels supplying the membrane of the sinus and the dura. The floors of the frontal sinuses separate them from the orbits. These floors are made up of thin bone similar to that of the posterior walls. The only communication of the frontal sinus cavities with the outside world is by way of the small and sometimes tortuous nasofrontal ducts opening just under the anterior tip of the middle turbinates.

Pathologically, acute frontal sinusitis begins with an inflamed membrane lining and formation of pus. The nasofrontal duct may then become blocked by swelling, polypoid tissue, or thick secretions. Pus under pressure may then extend in 3 main directions: (1) Infection may extend into the thin compact bone of the posterior wall of the sinus causing an osteitis. Vascular perforations may then allow extension into the cranial cavity. (2) Infection may extend into and through the thin compact bone of the floor of the sinus causing orbital swelling, cellulitis, or abscess. (3) Infection may extend into the diploic bone of the anterior wall causing an osteomyelitis. Perforating vessels may later carry the infection into the cranial cavity.

The principal cause of acute frontal sinusitis is upper respiratory infection. Do not forget, however, that swimming and trauma may cause acute frontal sinusitis, often of a fulminating type.

Acute frontal sinusitis usually develops in a fairly uniform pattern, although time intervals are variable. The patient has a head cold for several days to a week or more before localized pain begins in one or both frontal sinuses. Nearly always a preceding or coexisting purulent nasal or postnasal discharge occurs. This condition is a vital point in the history and examination. Discharge may decrease or stop when the sinus ostium becomes obstructed and pain then develops. Partial obstruction of the nasofrontal duct usually causes mild pain and tenderness over the involved sinus, tending to occur after arising and to subside in the evening or after lying down. The pain is not too difficult to control and edema is not present. At this stage, treatment may be conservative.

Danger signals may arise after one or several days, and the infection must then be regarded as potentially serious. The pain may become much more intense, perhaps suddenly, and is difficult to control. The pain is constant, may be worse at night, and may be associated with generalized headache. The patient is irritable, anxious, and ill. Normal temperature should not be misleading, since fever may be slight. Tenderness over the frontal sinus tends to become exquisite. Edema of the lids may appear. At

CHARLES B. PORTER, *a 1939 graduate of Johns Hopkins University School of Medicine, is a specialist in otolaryngology and is on the staffs of Deaconess and St. Michael's hospitals, Grand Forks, North Dakota.*

this stage, no time should be lost in careful examination of the nose, throat, and sinuses with roentgenograms if needed. Vigorous treatment attempts to control infection and to establish drainage, surgically if necessary.

The most ominous group of symptoms are those associated with continued total blockage of the nasofrontal duct with empyema of the frontal sinus. The lids or orbital contents may become swollen and inflamed, indicating orbital extension. The forehead overlying the frontal sinus may become edematous indicating underlying osteomyelitis. The temperature may rise considerably. Most ominous signs of all are those indicating intracranial extension, such as generalized severe headache, nuchal rigidity, reflex or motor changes, delirium, or convulsions. This group of patients usually requires surgical treatment.

Diagnosis is made by history, frontal sinus tenderness, and nasal examination. If blockage of the sinus is incomplete or if other sinuses are involved, the nose will be congested and contain pus, or pus will be seen in the nasopharynx. If blockage of sinuses is complete, the nose may appear almost normal. The involved sinus usually transilluminates poorly and roentgenograms usually appear cloudy. As I have stated before, a history of preceding or coexisting purulent nasal discharge is strong evidence of sinus infection. It is worth noting that sometimes frontal sinus tenderness is much better demonstrated by upward pressure on the thin floor of the sinus than by pressing or tapping on its thick anterior wall. In severe cases, the white blood cells may be elevated. Increased spinal fluid cell count is obviously a serious sign; if the count is high, meningitis and/or brain abscess are suspected. A neurologic examination should be done. Edema of the skin of the forehead is almost certain evidence of osteomyelitis of the frontal bone and requires surgical treatment.

Before discussing treatment of frontal sinusitis, I would like to underscore 3 important facts to be kept in mind when diagnosing serious frontal sinus infections. First, antibiotic therapy may result in much less severe symptoms even though the disease is progressing. This condition may be called masked sinusitis. A patient responding more slowly than usual to treatment for acute frontal sinusitis should be watched closely for even weakly positive signs of complete frontal duct blockage. The masking of symptoms of mastoid infection by chemotherapy or antibiotics has been known for many years. Similar, though less frequent and less pronounced, masking of the symptoms of sinus infection may occur as a result of antibiotic treatment of respiratory infections or mild sinusitis. Second, patients of cheerful and matter-of-fact temperament with relatively high pain thresholds may be more ill than they appear. Conversely, hypersensitive patients with minor sinus disease may complain bitterly and seem to exhibit extreme frontal sinus tenderness. Third, frontal sinusitis may be very fulminating, reaching the stage of serious complications, such as meningitis, within a few hours. This is especially true of frontal sinusitis consequent to swimming and diving.

Treatment of acute frontal sinusitis depends on its severity. Primary precautions are adequate bed rest and avoidance of exposure and chilling. Alcohol and tobacco are temporarily forbidden. Adequate humidity is advisable and local dry heat is applied to the forehead two to four times daily for thirty minutes. Penicillin or another antibiotic is prescribed in adequate dosage. Codeine relieves pain and nasal congestion. I do not prescribe nose drops because of their congestive after effects. If used, a mild and dilute form such as 0.5 per cent ephedrine in normal saline is best. Elevation of the head on two pillows helps frontal sinus drainage. The Proetz displacement treatment I find very useful. Preliminary vasoconstriction with 2 per cent ephedrine and 0.5 per cent cocaine spray or cotton pack may be used in the office or hospital. The current solution in use in our clinic consists of a solution of polymyxin, 1,250 units per cc., and gramicidin, 50 units per cc., in normal saline. Just before use, 2 cc. of 0.5 per cent Pyribenzamine nasal solution is added to 15 cc. of the antibiotic solution. Proetz displacement is done every day or two until relieved.

In cases of frontal sinusitis showing persistent signs of frontal duct obstruction and failing to respond to the treatment just outlined, a drainage operation is indicated. The simplest procedure is to make a trephine hole through an incision in the medial portion of the eyebrow. Roentgenograms should be taken first to make sure that a frontal sinus is present and to determine its size. A nose forehead view is needed for this purpose plus a lateral view to estimate the thickness of sinus walls. After trephining, a small mushroom catheter is inserted. This can be very gently irrigated with dilute antibiotic solution. Never use force as severe meningeal reactions have resulted from such irrigations. When solution passes freely into the nose through the

nasofrontal duct, the catheter can be removed.

Cases of frontal sinusitis with osteomyelitis or intercranial involvement require the radical frontal operation with removal of diseased bone and drainage of extradural or subdural abscesses, if present. If necessary for bone disease, the sinus may be permanently obliterated and plastic reconstruction done after the patient has been well for six to twelve months. I usually pack an extradural abscess with an iodoform gauze strip which is gradually removed over a period of one to three weeks to prevent obstruction of the drainage pathway.

I wish to present a case of acute frontal sinusitis with grave complications. The symptoms in this case were considerably suppressed by Aureomycin, although the patient probably owes his life to the drug. It is worth noting that the patient is a husky, cheerful, uncomplaining farm boy with a high pain threshold.

CASE REPORT

A husky, 16-year-old farm boy contracted a cold on June 20, 1950. Within a few days he developed frontal pain and tenderness. He was treated with penicillin every three hours in a Minnesota hospital. He left the hospital on July 6, 1950, and was treated as an outpatient for three weeks because of recurrent frontal headaches. He was given an unidentified pain pill which gave fairly good relief. However, on July 28, 1950, about five weeks after the onset of his illness, the boy became mentally fuzzy and slow and then delirious. He was hospitalized in Minnesota and given intravenous fluids and again multiple antibiotics were administered in adequate dosage with sulfa drugs as well. On July 30, 1950, he had convulsive movements of the right arm and leg.

The patient was transferred to the Deaconess Hospital in Grand Forks by ambulance on July 31, 1950. The physical examination showed a 16-year-old boy, well developed, but responding very sluggishly and not very accurately. At times he seemed almost comatose. He was able to move the left arm and leg but not the right arm and leg. The ears were negative. The nose was mildly congested with a slight clear mucoid discharge on the left. There was no sinus swelling, no swelling of the eyes, no redness, and no apparent sinus tenderness. The throat was clear. The tonsils were small. The pupils reacted to light. A flaccid paralysis of the right arm and leg was present with absent tendon reflexes. Right abdominal reflexes were absent, and a right Babinski test was positive. The left knee and ankle jerks were depressed but tendon tone was present. There was a right facial paralysis and many facial grimaces on the left. A definite meningismus was present. Neurologic examination thus indicated a focus on the left which was extensive enough to be internal capsule involvement spreading also to the right. X-ray examination of the paranasal sinuses showed dense clouding of both antral and frontal sinuses. The ethmoids were partially clouded. Small areas suggesting destruction appeared in the left frontal bone well above the region of the left frontal sinuses.

Spinal puncture showed initial pressure of 220 mm. of water and a final pressure of 140 mm. of water. Cell count on the spinal fluid showed 15 segmented cells, 4 lymphocytes, and 1 red cell. Protein was 54, sugar 72 mg. per cent, and white blood cells 30,000 with 80 per cent neutrophils. The hemoglobin was 66 per cent, and the urinalysis was essentially negative. Serologic test for syphilis was negative. The spinal fluid was cultured and showed no growth. Colloidal gold curve was normal.

While in the hospital the patient ran a rectal temperature as high as 103.4° of a spiking type. In view of the history of sinusitis and the indication of serious brain damage on the left, it was decided that exploratory operation on the left frontal sinus was indicated. The tentative diagnosis was left frontal sinusitis with osteomyelitis and possible sagittal sinus thrombosis with or without brain abscess.

On August 1, 1950, left external frontal operation was performed under local anesthesia. The frontal was entered through the anterior plate, most of which was removed. The sinus was found to be full of creamy pus with a granular lining. The duct was blocked by granulations. These were removed and an adequate bony opening was made into the nose. A bony defect about 3 mm. in diameter was found in the posterior wall of the left frontal sinus. This was plugged with granulations. Most of the posterior wall of the frontal sinus was removed. About 2 cc. of pus welled from an epidural abscess when the granular dura was exposed. A tract of granulations led toward the sagittal sinus. No defect was found in the dura and no fluctuation was felt. Hence, the dura was not opened. Fairly normal dura was exposed with wide removal of much frontal bone. The limits of infected bone were difficult to determine since it was not typically avascular. One double-small Penrose drain was inserted and the wound was closed after application of sulfa penicillin powder to the sinus in the wound. Culture later showed nonhemolytic gram-positive diplococci.

Postoperatively, the patient responded rapidly. The temperature dropped quickly. Within five days the temeprature was entirely normal and remained so for the rest of the stay in the hospital. Aureomycin was given both intravenously and orally along with large doses of penicillin intramuscularly. Because we felt that thrombosis of the sagittal sinus or of its large tributaries was possibly present, we administered dicumerol from August 2 to August 17. The patient was given Dilantin to control his occasional focal convulsions of the right arm and leg. On August 8, 1950, the patient recovered function of the right leg and right side of the face. Considerable aphasia persisted for some time, however. By August 27, 1950, the patient was walking downtown and back and was speaking more and more each day. His objective condition seemed fine. He was dismissed on August 27, 1950, to be maintained on 250 mg. of Aureomycin five times daily at home. This medication was continued for three weeks.

The patient remained relatively free of symptoms until September 27, 1950. At this time, he experienced a mild right-sided convulsion with fever, transient weakness of the right arm and leg, and mild and transient frontal headache. The recurrence of convulsions we felt to be an alarming symptom. The patient was readmitted to the Deaconess Hospital on September 27, 1950. No evidence of recurrence of sinus disease was found,

but examination led us to believe that our patient probably had a brain abscess with or without sagittal sinus thrombosis. Because of this probability, he was referred to the University of Minnesota Hospital for diagnosis and further treatment. The patient was operated on October 4, 1950. At operation, an extensive osteomyelitis of the frontal bone was found extending up along the sagittal sinus. A brain abscess was encountered on exploration of the brain just anterior to the motor cortex area. This abscess was drained and opaque medium was inserted so that the course of the abscess could be followed by x-ray. A very large hydrocephalus of the left cerebral hemisphere was found. This condition was thought probably to be due to sagittal sinus thrombosis.

The patient did well postoperatively except for rather stubborn and frequent convulsions which were controlled with adequate doses of Dilantin. Unfortunately, the patient developed further sinus difficulties on the right side and on October 23, 1951, the right frontal sinus was trephined and drained. He did well for a period of nearly two years with use of Dilantin for convulsion control. The brain abscess showed good resolution and became quite small. However, on July 23, 1953, a severe acute right frontal sinusitis developed requiring radical frontal operation on the right side. The patient's recovery from this operation was good and he has remained well to the present time.

The patient was last seen on November 7, 1953, at which time he was ambulatory, getting by in his schoolwork, and showed no serious residue of his right-sided paralysis. The sinuses showed no evidence of infection.

Analysis of the foregoing history indicates that the patient was under outpatient treatment elsewhere for three weeks, during which time he had only mild pain which was easily controlled by oral analgesics. Despite this therapy, he developed a frontal osteomyelitis, an epidural abscess, and a brain abscess or sagittal sinus thrombosis or both. Apparently intensive penicillin therapy greatly diminished the pain and constitutional symptoms to be expected with this boy's illness. Pain was always mild and no local tenderness or edema of the overlying skin occurred. Sinus roentgenograms taken on admission to the Deaconess Hospital six weeks after the initial coryza showed a 1 by 2 cm. area of osteomyelitis of the left frontal bone. It is well known that x-ray changes in such cases are about ten days behind the clinical extent of bone disease. After radical surgery for frontal sinus infection and removal of diseased bone, Aureomycin therapy was capable of controlling infection in such a way that hemiplegia cleared entirely and no symptoms of frontal bone osteomyelitis or brain abscess occurred for two months after surgery, even though the process was apparently active during that time. It is noteworthy that despite presence of an epidural abscess and a brain abscess, the spinal fluid cell count on two occasions did not exceed 23 cells per cubic mm. Ordinarily brain abscesses should show a much higher count.

SUMMARY

1. Acute frontal sinusitis is discussed; serious complications are given special attention.

2. Antibiotic therapy may suppress or mask symptoms of serious sinus disease.

3. A case of frontal sinusitis with severe complications is presented. Symptoms were partly masked by antibiotic therapy.

Current Literature on Pain

EXSUFFLATION WITH NEGATIVE PRESSURE, by Alvan Barach and G. J. Beck. Arch. Int. Med. 93: 825-841, 1954.

"Of the various physical methods developed for eliminating bronchial secretion, exsufflation with negative pressure was recently reported as the most effective. . . . The purpose of this paper is to present the effect of E.W.N.P. as a therapeutic agent in patients with poliomyelitis and other neurological disorders, bronchial asthma, pulmonary emphysema, bronchiectasis, postoperative pneumonia, and pulmonary atelectasis. . . . A series of 103 patients with respiratory difficulties and retention of bronchial secretions were treated with 106 courses of E.W.N.P. . . . The principle of this mechanical method of eliminating mucus or mucopurulent sputum depends on a marked inflation of the lungs and bronchial tree by an inspiratory pressure of 30 to 40 mm. Hg followed by a rapid drop in pressure to 35 to 40 mm. Hg or more below atmospheric pressure. The total pressure drop, of 65 to 80 mm. Hg, in a period of approximately 0.02 seconds, results in expiratory flow rates of a sufficiently high order of magnitude to blow secretions from the lungs. Expiratory flow rates, of 10,000 cc. per second, produced by a high-speed motor blower unit, are frequently two to five times higher than those obtained in coughs of maximal effort in patients with respiratory difficulties.

"The clinical use of E.W.N.P. in cases of poliomyelitis and other neurological diseases with breathing difficulties appeared to be of critical value in 20 of 22 patients and responsible for the clearing of pulmonary atelectasis in 11, for removal from the respirator in 4, and for marked relief of obstructive breathing in all 20. Marked benefit was also observed in seven patients in whom bronchoscopic suction or tracheotomy followed by suction by catheter had previously proved ineffective. Clinical improvement of significant extent, manifested by relief of dyspnea and cough, was observed in 22 cases of bronchial asthma and 43 cases of pulmonary treatment with E.W.N.P. in four cases. The elimination of retained mucopurulent sputum by means of E.W.N.P. was, at times, an effective method of relieving obstructive dyspnea, and, in cases in which accumulation of bronchial

(Continued on page 466)

Editorial

NEW DRUGS FOR CONTROL OF CHRONIC PAIN

Currently an abundance of drugs are available for patients who are distressed either by physical pain or mental pain. Those who must deal with patients who are suffering from these distractions, must have a number of approaches to the solution of the problem. If drugs are to be employed, it is important to consider the choice of the drug from several points of view so that, if, for example, the pain is chronic, an addicting drug will be avoided, whereas such a drug need not be avoided when pain is acute and is to be used for preliminary medication before anesthesia and operation.

Some interesting new drugs give us confidence that we will be able to deal with chronic pain without producing addiction. Such a drug is heptacylazine (WY-401 or 1-methyl-4-phenyl-4-carbethoxy-hexamethyleneimine hydrochloride), which is strictly an analgesic. Having no other apparent drug effects, such a drug may be used alone or combined with other drugs such as aspirin in the case of inflammatory pain or with chlorpromazine. It also seems timely to mention the possibility of using a combination of drugs for relief of distress so that very large doses of one agent need not be used. It is not meant to exclude the well-known methods for relief of pain but merely to call attention to the fact that these newer drugs fill a need which has existed for a very long time.

John S. Lundy, M.D.

Book Reviews on Pain

SELECTION OF ANESTHESIA: THE PHYSIOLOGICAL AND PHARMACOLOGICAL BASIS, by John Adriani, M.D., director, department of anesthesiology, Charity Hospital; professor of surgery, School of Medicine, Tulane University of Louisiana; and clinical professor of surgery and pharmacology, School of Medicine, Louisiana State University, New Orleans, Louisiana, 1955. Springfield, Illinois: Charles C Thomas, 327 pages. Price $6.50.

This book was prepared with the objective of being useful to those who are concerned with anesthesia, but who do not administer anesthetic agents. This objective, then, would apply to physicians and surgical specialists and to consultants who are charged with the management of postoperative complications, and it should be embraced also by physicians and nurses who are undergoing training in anesthesiology.

The book has three parts: the first deals with the pharmacologic and clinical application of drugs; the second part has to do with diseases and their relationship to anesthesia; and the third part treats the relationship of anesthesia to the operation to be performed.

Generally speaking the book is a compilation of facts well known to the author but probably not to the reader for whom the book is intended.

Some miscellaneous digressions which have no demonstrable basis in orderly thought are to be noted, such as, "Combinations of routes and drugs are widely employed in current practice. This practice, for some reason which has no scientific basis, has been termed by certain anesthetists, *balanced anesthesia.*"

Why this provocative pronouncement has been included leads one to ask what profit can be gained from buffeting a straw man? Whoever said that the term, *balanced anesthesia*, was based on science? Is a *balanced diet* scientific? Is a *balance of power* scientific?

An excellent table is presented which shows the general properties and characteristics of anesthetic drugs currently employed.

The book is printed on good paper, is easily read, and is well illustrated and well indexed. It should serve well the purpose for which it was intended. The material in the book obviously is a compilation of material used by the author in his teaching. It can hardly be said, however, to include much worthwhile material from other sources, but since there is no other book of its kind in existence, it derives value from that fact. It should appeal strongly to those who are concerned with the author's opinions and practices.

John S. Lundy, M.D.

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MIGRAINE AND PERIODIC HEADACHE: A MODERN APPROACH TO SUCCESSFUL TREATMENT, by Nevil Leyton, M.R.C.S., L.R.C.P., honorary physician, Migraine Clinic, Putney Health Centre; clinical assistant, King Edward VII Hospital, Windsor, 1954. London: William Heinemann Medical Books, Ltd. Second edition, 128 pages. Price $2.50.

It is said that Diogenes, when asked what he would take to let a man give him a blow on the head, replied with succinct wisdom: "A helmet." Hence, a hearty welcome awaits a book such as Leyton's, which depicts a story of success in treating a condition which has resisted all attempts at relief since the time of Diogenes and his practical prophylaxis. The author maintains that periodic headache, whether it is called migraine or not, can be treated with good results in more than 75 per cent of cases. Most of the patients, after their distress has been classified and treated according to the author's plan, very soon show signs of almost complete relief. Some require only short treatment; others require long treatment.

Where there is an effect, there usually is an agent, and the particular agent which the author speaks about at length is anterior pituitary-like hormone, which is prepared from urine obtained during pregnancy and is not neutralized by the action of cysteine. The anterior pituitary-like hormones used by the author are Antuitrin S and Pregnyl. He often desensitizes the patient with neostigmine, but depends on injections of histamine when the condition is more difficult. He suggests the injection of vitamin B_2 compound for patients in whom neuritis complicates the picture. He does not disregard carbaminoylcholine chloride (carbachol), urea or bellergal, but feels that they are to be used only when the condition is complicated, that they cannot be depended upon to do much by themselves.

At this stage, our chief interest is in his results. He writes that among 2,279 patients he obtained complete relief for 563; for 1,298, the attacks were much reduced in severity and frequency; for 326, he achieved some improvement; and for 92, he could do nothing. He considers that from 4 to 9 per cent of white people in the world suffer from migraine, an observation which, if sustained, would mean that millions of people are more or less incapacitated for comfortable and effective living. The author feels that this is unnecessary. Not only that, he writes that it is downright cruel to tell a woman at 25 years of age that her headaches will disappear at 50, when the menopause is upon her, but that until that physiologic sequel she must look forward to twenty-five years of suffering. Actually, he says, the situation is different, and he tells why.

It is difficult to find fault with the presentation of the author's plan for a therapeutic approach to periodic headache. On one point, however, there should be some sober reflection. The author believes that intradermal tests done with histamine are reliable, a contention which is not admitted in this country. Current research indicates that intradermal injections of histamine are so thermolabile that in a warm room they will almost always give positive results in any patient.

The report of cases are beautifully presented and are fascinating reading, as are so many papers written by Englishmen.

If each practicing physician could have a copy of this book and would read it, he probably would translate the author's principles into effective action. The result could be one of the most beneficial occurrences since the evil day when man first got a pain in the head. For that reason, as said before, it deserves a great welcome.

JOHN S. LUNDY, M.D.

CURRENT LITERATURE ON PAIN

(Continued from page 464)

secretions appeared to maintain bronchopulmonary infection, this technique seemed to aid the management of respiratory infection by promoting a more efficient bronchial drainage than the patient himself was able to provide. The vital capacity of 12 patients with bronchial asthma increased 15 per cent, that of 34 patients with pulmonary emphysema increased 42 per cent; that of 4 patients with bronchiectasis increased 39 per cent; and that of 4 patients with neurological disorders increased 25 per cent after one treatment with E.W.N.P. and bronchodilator aerosols. Repeated courses of E.W.N.P. resulted in a mean rise in vital capacity of 55 per cent in eight patients with neurological disorders and of 24 per cent in nine patients with pulmonary emphysema and bronchial asthma. The use of E.W.N.P. in patients with bronchial asthma and pulmonary emphysema, in whom retention of secretions played a less important role than bronchospasm, was accompanied by little or no benefit. The clinical indications for the use of this procedure depend on whether or not functional pathology is produced by inadequate elimination of mucus or mucopurulent sputum from the respiratory tract."

From LUNDY, J. S., and MCQUILLEN, FLORENCE A.: Anesthesia Abstracts. Minneapolis: Burgess Publishing Company, 1954, Vol. 40. Copyright by J. S. LUNDY.

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LOWER ABDOMINAL PAIN IN THE POLY-SURGICAL PATIENTS, by R. H. BARRETT. Anesth. & analg. 33:326-332, 1954.

"Dietitians have suggested combining training and use of certain drugs to adjust the 'appestat' in order to avoid obesity. With that in mind, it was suggested, recently, that the anesthesiologists develop an 'algestadt' to raise or lower the pain threshold. . . . The surgical patient who still has, and still complains of that same lower abdominal and low back pain presents a challenging problem—especially since she has had a dilation and curettage, and oophorectomy and incidental appendectomy, a uterine suspension, a myomectomy, a hysterectomy, another oophorectomy and 'freeing-up of adhesions' and a mid-line exploratory operation, in more or less that sequence over a period of months or years. This is the type of problem case that is often relegated (and I use the term advisedly) to the anesthesiologist. In considering this relatively complex pain problem it is necessary to spend an appreciable length of time with the patient listening to the description of her problems. A first hand description is practically always preferable to a review of her written history—although the two should be correlated. . . .

"In considering treatment for the relief of pain in the poly-surgical case—and, except for this presentation this symptom complex is, by no means, limited to the female of the species—it must be kept in mind that all probable and often all possible organic abnormalities have been eliminated, in so far as the acumen of any particular physician or group of physicians is concerned. . . . Therapeutic nerve blockade for the relief of pain has been an important function of the practice of anesthesiology since the modern inception of this specialty. Results of this form of therapy depend on: choice of patient, interpretation of signs and symptoms, technic of blockade in regard to anatomical location, as well as timing, and agents used. Generally speaking, the results obtained by this form of therapy are directly proportional to the insight, of the operator, into the situation at hand and the rapport which exists between the patient and himself—a relationship certainly not unlike that sought in other fields of medicine. . . . Actually, the cause of all pain, except that due to direct nerve trauma, is probably ischemia of some degree. Ischemia may be due to either vasospasm or vasodilation. In the poly-surgical patient it is almost invariably due to vasospasm.

"Vasospasm in the lower abdomen of the female may be due to any or all of several factors, such as: (1) hormonal disorders—or even orders—associated with the menstrual cycle, (2) structural changes due to osteoembolus or thrombus, (4) trauma resulting from external or internal factors. Here would be included (a) broken bones of low back or pelvis, (b) hemorrhage (internal), and (c) various surgical operations. All or most of these conditions will have been considered before instituting treatment of pain, per se, in the patient in question. There is, however, one form of vascular trauma which probably accounts for more pain in the human body than anything that has yet been mentioned. That is reflex trauma. This form of trauma is concerned with persistent bombardment of the sympathetic nervous chain by afferent stimuli from damaged or diseased peripheral tissues until in some poorly understood fashion the reflex pattern becomes self-perpetuating. It is with the upset of this self-perpetuating reflex pattern that the anesthesiologist is concerned primarily in his treatment of pain. . . .

"The factor which is easiest to remove is that of vasospasm. This can be accomplished in at least three ways: (1) general blockage of all autonomic ganglia with tetraethyl ammonium chloride (Etamon), ethyl alcohol, procaine, Priscoline, hexamethonium or benzazoline. (2) More specific blockade of the rami communicans may be achieved by spinal or caudal or epidural anesthesia. (3) The most specific blockade is accomplished by direct anesthetization of the lumbar sympathetic ganglia by the paravertebral approach."

From Lundy, J. S., and McQuillen, Florence A.: Anesthesia Abstracts. Minneapolis: Burgess Publishing Company, 1954, Vol. 40. Copyright by J. S. Lundy.

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EXPIRATORY POSITIVE PRESSURE OXYGEN THERAPY IN CHRONIC PULMONARY DISEASE, by W. O. Arnold. J.A.M.A. 155:1329-1331, 1954.

"Oxygen therapy is not necessary for all patients who have chronic pulmonary dysfunction. Patients with ventilatory insufficiency do not require oxygen unless there has been progression of their disease or a crisis precipitated by infection, excessive activity, or other causes. Patients who have severer and more advanced impairment of alveolar ventilation or pulmonary dysfunction with cardiac insufficiency, however, do require oxygen. . . . . Oxygen given by means of ordinary face masks, tents, and nasal catheters has been used in treating patients with chronic pulmonary disease for years, but results are unsatisfactory in almost all cases. In the last four or five years, oxygen given with intermittent positive pressure (inspiratory) has been utilized. . . . . For the past 19 months, we have prescribed expiratory positive pressure oxygen therapy for continued daily use by patients with the severer and more advanced forms of chronic pulmonary dysfunction. During this time 36 such patients have been treated. Initially nine of our patients had heart failure on the right side, and one of these also had carbon dioxide acidosis. . . . . The apparatus used was the O.E.M. meter mask, which is metered for expiratory positive pressure. . . . .

"The use of expiratory positive pressure oxygen therapy in the management of 36 patients with varying types of chronic pulmonary dysfunction, nine of whom had heart failure on the right side and one of whom also had carbon dioxide acidosis, brought about marked improvement in 17 patients (including the patient with carbon dioxide acidosis); moderate improvement in 18 patients; and no change in one patient. Follow-up studies covering a period of 19 months revealed further improvement in 19 patients and maintenance of the original improvement in 8 others; 2 patients were worse, 5 patients had died, and no data were available for the other 2. A complementary program to be continued daily in the home is important."

From Lundy, J. S., and McQuillen, Florence A.: Anesthesia Abstracts. Minneapolis: Burgess Publishing Company, 1954, Vol. 40. Copyright by J. S. Lundy.

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CARDIAC ARREST, by Brian Blades. J.A.M.A. 155: 709-712, 1954.

"Accumulated data from various clinics and studies of large series of anesthetics and operations suggest that a fair average figure for the incidence of cardiac arrest might be one in 5,000 cases. . . . . At the George Washington University Hospital only two cardiac arrests occurred in 42,636 operations in the period between 1948 and 1952. There were none in about 7,000 operations in 1953. Precise evaluation of the number of cases in which true cardiac arrest develops is difficult, because in all types of sudden death the heart eventually stops. It would seem safe to assume that in some cases sudden cessation of the heartbeat in the operating room or during induction of anesthesia results from coronary occlusion, pulmonary emboli, or other factors and that these are not true examples of sudden cessation of cardiac function from the effects of anesthesia or surgical manipulation. . . . .

"Successful prevention of cardiac arrest requires knowledge of the physiological principles involved. Anoxemia is the common denominator. . . . . All anesthetic agents are insidious poisons, if mishandled. It is probably not so much the agent but how the agent is employed that counts. . . . . The maintenance of the circulation must be considered in terms of circulating blood volume and adequate oxygenation of the blood at all times. . . . . It is possible that many instances of cardiac arrest could be prevented if proper precautions were maintained. The grave consequences of the combination of anoxia and a high level of circulating epinephrine on cardiac function can be produced both in the operating room and the laboratory. The fearful patient subjected to a hurried induction of anesthesia or to too much anesthetic agent in the absence of oxygen may be expected to behave in the same manner as the laboratory animal who is partially suffocated deliberately and at the same time given epinephrine experimentally to produce ventricular fibrillation or cardiac standstill. It is safe to predict that the extensive teaching program on the prophylaxis and treatment of cardiac arrest will reduce its incidence. It is of prime importance that the relative infrequency of this complication and the educational program of prevention and treatment be known to the public so that necessary operations will not be refused by patients terrified by newspaper accounts."

From Lundy, J. S., and McQuillen, Florence A.: Anesthesia Abstracts. Minneapolis: Burgess Publishing Company, 1954, Vol. 40. Copyright by J. S. Lundy.

American College Health Association News . . .

NEW MEMBERS

We are very happy to welcome the following new member whose application has been approved by the Executive Committee:

Valparaiso University, 351 College Avenue, Valparaiso, Indiana. Representative: Irene Weihl, R.N., B.A., associate director, Health Service.

PERSONNEL

Dr. Warren E. Forsythe, who recently retired from his post as director of Student Health at the University of Michigan, sends his new address. Dr. Forsythe can be reached at: 2667 Chula Vista Boulevard, Eugene, Oregon.

John W. Brown, M.D., president of the American College Health Association, has appointed the following council members to serve on the Executive Committee for the year 1955-56: Norman S. Moore, M.D., past president, director, Student Health Service, Cornell University, Ithaca, New York; and Donald S. MacKinnon, M.D., director, Student Health Service, University of California, Los Angeles, California. Other members of the Executive Committee include, according to the constitution, the president, John W. Brown, M.D.; the president-elect, Paul L. White, M.D.; the vice-president, Helen Rossiter, M.D.; and the secretary-treasurer, Irvin W. Sander, M.D.

Secretaries of local sections are reminded to send lists of officers and the program or reports of local section meetings to the Secretary for the records of the association and for inclusion in the News Notes.

Written request should be directed to the Secretary after local section meetings for reimbursement from the national group to the local section for each member who belongs to both the local and the American College Health Association. These refunds will be made only on written request.

Intestinal Obstruction, by Owen H. Wangensteen, M.D., 1955. Springfield, Illinois: Charles C Thomas. Third edition, 838 pages. $15.50.

This important book has been extensively revised and enlarged in its third edition. Significantly longer than the second edition, additions include: descriptions of new technics; a linking of new information, such as a better understanding of fluid and electrolyte balance to the specific problems of bowel obstruction; and a carefully tabulated review of the results of treating bowel obstruction at the University of Minnesota. All the sections have been brought up-to-date. Throughout the book both the old and the new have been carefully examined and evaluated in light of the author's unexcelled experience.

Even the hurried scanner of this volume should pause long enough at the beginning to read the preface. In it is an entertaining story of the difficulties the author encountered in getting not only the first edition of the book, but also, earlier, his first paper on the suction treatment of bowel obstruction, accepted for publication. It sounds a welcome note of encouragement to any man blessed with an unconventional idea.

In a sound introduction to the problem, the first part of the book concerns the pathologic physiology of obstruction. Evidence is well presented to support an essentially "mechanistic" rather than a "toxic absorption" concept to explain the ill effects of obstruction. It is clearly shown that particularly in low, nonstrangulatory obstructions, the local effects of distention play the principal role.

The second part is on diagnosis, which includes a good classification of obstructions and a critical evaluation of the various diagnostic methods. The discussion of x-ray diagnostic technics is especially noteworthy. The author puts considerable emphasis in this section and throughout the remainder of the book on the sign of *intestinal colic* (auscultation of borborygmi occurring simultaneously with the peak of abdominal pain). To other observers this sign may not appear to be quite so important. Therefore, the author's point would have been considerably strengthened if the incidence of this sign had appeared in his tables. In the tables, however, bowel sounds are only described as increased or normal, on the one hand, and as decreased or absent on the other.

The impossibility of always differentiating strangulating from simple obstructions is convincingly illustrated. This fact, the author points out, must limit employment of the nonoperative management of obstruction. A policy is advocated of operating upon even the apparently simple mechanical obstructions if twelve hours of suction has proved to be ineffectual. This is a sound therapeutic plan which has as its only reasonable alternative, surgery for every case of obstruction.

The third part of the book reveals the broad requirements of good therapy for bowel obstruction. The subject is admirably handled. These chapters contain some of the author's contributions on a variety of important topics, such as anastomotic technic, which have, in addition to their value in bowel obstruction, a far wider application in general surgery.

The final section, on the speeial obstructions, is a lucid review dealing with each type of obstruction separately, beginning with the congenital obstructions. Throughout this section the historie growth of understanding and the development of treatment for each type of obstruction are well described. Many of the challenging problems that still face the student and investigator are pointed out.

(Continued on page 34A)

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BOOK REVIEWS

(Continued from page 468)

Like its earlier editions, this book should prove to be a valuable guide and counsel to any physician who encounters, even occasionally, a patient with bowel obstruction.

F. JOHN LEWIS, M.D.

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Atlas of Roentgen Anatomy of the Skull, by LEWIS E. ETTER, M.D.; with a section on *The Radiographic Anatomy of the Skull in the Newborn Infant,* by SAMUEL G. HENDERSON, M.D., and LOUISE S. SHERMAN, M.D., 1955. Springfield, Illinois: Charles C Thomas. 215 pages, 239 plates. $14.75.

This work represents the results of a specific type of roentgen anatomic research as applied to the skull. The various bones of the skull have been disarticulated and photographs of roentgenograms of the bones have been taken in various projections. This is supplemented by photographs and roentgenograms of the remainder of the skull without the various components. This helps to clarify various lines and shadows depicted in roentgenograms of the skull as a whole, paranasal sinuses, facial bones, and temporal bones. The chapters on the temporal bone and the skull in the newborn infant are useful supplements.

The atlas type of presentation is carried out in admirable fashion. The photographs and roentgenograms are quite clear, and a special method of labeling the photographs and roentgenograms directly adds to the clarity of presentation and makes the work of the reader less tedious.

This volume merits the study of the large variety of medical specialists, including the anatomist, radiologist, otolaryngologist, neurosurgeon, and oral surgeon.

CHARLES M. NICE, JR., M.D.

•

The Human Adrenal Cortex, Ciba Foundation Colloquia on Endocrinology, edited by G. E. W. WOLSTENHOLME, and MARGARET P. CAMERON, 1955. Boston: Little, Brown & Co., Vol. 8, 655 pages. $10.00.

This monograph presents 36 papers which are discussed by more than 60 leading research workers from 8 countries.The subjects treated range from the histochemistry of the adrenal cortex to the psychologic responses to the administration of ACTH and cortisone. Current knowledge concerning methods of studying adrenal function in man and all of the major human diseases involving cortico-adrenal dysfunction are included. The volume is superior to many symposium reports in that it is well indexed, well illustrated and well documented.

Each of the sections is informative, but clinicians will probably be most interested in such new studies as those of hypophysectomy for metastatic breast cancer and in severe diabetes mellitus, in both of which situations encouraging amelioration was seen.

The Ciba Foundation, which supported the symposium, is a nonprofit trust founded in 1947 by the chemical and pharmaceutical firm of the same name, and has arranged 29 symposia in various areas of medicine in its first five years of operation. It is to be congratulated upon its work.

MAURICE B. VISSCHER, M.D.

•

Cough Syncope, by VINCENT J. DERBES, and ANDREW KERR, JR., 1955. Springfield, Illinois: Charles C Thomas. 182 pages. $4.75.

This small volume has all of the characteristics of excellent medical writing. Historic discussion of its topic is given in a fascinating manner portraying the thoroughness and competence of the authors in gathering pertinent information. Inclusion of 36 concise case histories serves as an expedient means for conveying relevant data. Ample

(Continued on page 36A)

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(Continued from page 34A)

space is devoted to the differential diagnosis of related conditions. The chapter dealing with theories of the mechanism of cough syncope is rich in minute details and elucidating comments. In other chapters, exposition of the physiologic mechanism as well as the medicolegal aspects of cough syncope reflects critical insight and judicious objectivity.

Because of the noteworthy text, good bibliography, and precise artisanship in the production of this book, it is likely to enjoy great popularity with the medical profession.

ANDREW L. BANYAI, M.D.

•

Pomp and Pestilence. Infectious Disease: Its Origins and Conquest, by RONALD HARE, M.D., 1955. New York City: Philosophical Library, Inc. 224 pages. $5.75.

This is a charming little book which, while written simply enough so that laymen can enjoy it, is full of information that will interest and delight the physician, particularly the physician who is interested in the history of medicine. Dr. Hare not only tells about recent terrible epidemics, but he tells of the ancient epidemics which affected the course of history. He gives a helpful bibliography which shows how much reading and research he did in order to write the book. He tells of the 24,000,000 cases of typhus that raised havoc in Russia in the years 1918 to 1922; and of how smallpox, introduced into Mexico by the Spaniards, wiped out perhaps 350,000,000 Aztecs. Few persons not well read in epidemiology realize how rapidly many primitive people have been exterminated by the epidemics brought them by travelers.

Dr. Hare has an interesting chapter on remedies used in the past in an effort to conquer infection.

He says that plague largely disappeared from England after the 1660's, and from Europe during the eighteenth century, probably because of the virtual extermination of black rats by the disease. Dr. Hare says it is estimated that in India alone there are 100,000,000 attacks of malaria in a year; in China there may be 21,000,000 such cases. Smallpox is still rampant in these countries, and in one epidemic, as in 1943, cholera killed 400,000 persons in a fairly limited area.

On the last page of his book, Dr. Hare points out very wisely that before long the Orient is going to be faced with a terrible dilemma. With better sanitation, hundreds of millions of their children could be saved from death from parasitic infections and bacterial infections; but then they would be unable to save them from death by starvation.

WALTER C. ALVAREZ, M.D.

•

The Management of Endocrine Disorders of Menstruation and Fertility, by GEORGEANNA SEEGAR JONES, M.D., 1954. Springfield, Illinois: Charles C Thomas. 198 pages. $5.75.

Dr. Jones states in her foreword that she has written this monograph "for the medical student and physician, be he specialist or practitioner, who wishes in one place a brief review of the endocrine physiology of menstruation and fertility, as well as a survey of the principal endocrine disorders affecting these functions." She has done the job admirably. The first three chapters are devoted to the hormones concerned in reproduction and are excellent basic references concerning the history and present laboratory status of our knowledge. The clinical material in the ensuing chapters, which include a chapter on tumors of the chorion, is well organized. The diagnostic and therapeutic workup in terms of presenting symptoms and in terms of pathologic findings are systematically presented.

IRWIN H. KAISER, M.D.

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The Surgical Treatment of Epilepsy

LEONARD A. TITRUD, M.D., RICHARD B. TUDOR, M.D., and V. RICHARD ZARLING, M.D.

Minneapolis, Minnesota

Most individuals with convulsive disorders are brought to the physician during childhood for diagnostic investigation and treatment. The earlier in life that epilepsy can be controlled, the better the brain can be protected from the harm of anoxia, petechial hemorrhages, and other injurious effects of convulsions. As knowledge increases concerning the pathologic physiology of epilepsy, the more causes are found for the occurrence of seizures. Brain injuries, anoxia of childbirth, meningitis, encephalitis, tumors, cysts, and vascular and developmental anomalies of the brain and abscesses serve as frequent inciting causes of fits. The irritative epileptogenic focus is usually in viable cerebral tissue just adjacent to such a lesion. Frequently several such foci are distributed throughout the brains of epileptics.

The information gained from the type of seizure that the patient has, the abnormal findings of neurologic examination, the localizing defects apparent on skull roentgenograms, ventricular air roentgenograms, cerebral angiograms, and electroencephalograms serve to characterize the existent convulsive disorder. Hypoglycemic disorder must be identified in the differential diagnostic tests and treated properly. Intracranial irritative lesions such as depressed skull fractures, hematomas, tumors, cysts, abscesses, foreign bodies, and vascular malformations are best removed if possible. Medical management must be given a thorough trial in all continuing convulsive disorders. Uncontrolled seizures often induce cerebral tissue anoxia during the attack and even petechial hemorrhages from the accompanying hypertension. The cicatricial gliosis of the healing process of such lesions may in turn become epileptogenic. In this manner, the foci increase in number and the disturbance becomes even more unmanageable, with resultant physical, intellectual, and personality defects.

If the epileptic patient has seizures that cannot be controlled medically and if these convulsions are found to originate constantly from the same circumscribed area of the brain, cerebral surgery may serve as the treatment. These candidates have ordinarily been studied and treated medically for more than a year or two unless they have unmanageable status epilepticus. Several electroencephalograms must be consistently similar; the localizing quality of the epileptic aura, the nature of the seizure, and the abnormal neurologic findings should substantiate the electroencephalographic focus.

LEONARD A. TITRUD, *a 1936 graduate of the University of Minnesota, specializes in neurosurgery in Minneapolis.* RICHARD B. TUDOR, *a 1941 graduate of the University of Minnesota, specializes in pediatrics and is on the staffs of Northwestern, Abbott, Fairview, Swedish, and St. Barnabas hospitals, all in Minneapolis.* V. RICHARD ZARLING, *a 1943 graduate of the University of Minnesota, is a specialist in neurology and is clinical assistant professor of neurology at the University of Minnesota.*

When craniotomy is done, a large area of the brain about the epileptogenic focus is exposed. The operation is performed safely with the use of intratracheal anesthesia. An electrocorticographic study of the exposed cerebral cortex is done first. The electrodes which are placed over the brain surface serve to indicate accurately the irritative focus. Frequently, meningeal scarring is visible at such a site. Small and deformed gyri or degenerated brain tissue may be apparent. Infrequently, a depth electrode may have to be used to localize a subcortical focus. After the epileptogenic area has been accurately identified, its removal must be considered. If the area of brain concerned has an important function such as the motor cortex, this tissue is not excised unless the severity of the convulsions outweighs the resultant paresis which would result from surgery. In cortical excision, the tissue should be removed generously about and including the focus and extending moderately into the white matter. Larger arteries and veins should not be occluded or removed. After clean excision of the pathologic area, a careful electrocorticographic survey should be done again to be sure no abnormal areas remain; if they do, these must be removed also. These patients usually have a satisfactory convalescence. They are given small daily doses of phenobarbital or Dilantin for about one year after surgery.

Individuals having medically uncontrollable convulsive disorders and a definite localized epileptogenic focus that can be surgically excised satisfactorily have better than a 50 per cent opportunity of being cured of epilepsy. Approximately half of the remaining patients are definitely improved. Obviously, the results of this form of surgical treatment are very worthwhile.

The following brief case reports of 7 patients who were operated upon in private Minneapolis hospitals illustrate typically the problems encountered. It will be observed that the seizures usually begin in the first few years of life, and that the disabling nature of the ailment becomes apparent toward adolescence and adult life.

CASE REPORTS

Case 1. S.A., a 7-year-old white male was born one month prematurely with aid of forceps extraction after the mother had been in labor over a three-day period. Breathing was difficult after birth and oxygen was given. He was slow and under par and always seemed weak and flabby to the parents. Right leg jerking began at the age of 1 year. Tonic seizures with respiratory difficulty began at 3½ years of age. Electroencephalograms at 3½ and at 5 years of age were abnormal. Dilantin and Mebaral were used for treatment. The child suffered a cerebral concussion at 5½ years of age.

During hospitalization in January 1954 the physical and neurologic examinations were normal. Pneumoencephalogram on January 14 was normal. Electroencephalogram on January 11 was abnormal with slow wave and spikes maximum in the left temporal and occipital areas. The boy continued to have almost uncontrollable seizures with occasional unconsciousness. Clonic movements began in the right foot and progressed up the right side of the body to the face. Electroencephalogram on October 18, 1954, revealed a severe diffuse and paroxysmal dysrhythmia without a definite focus.

Craniotomy was done on October 19. Electrocorticogram revealed localized spiking over the left motor cortical foot and leg area. The arachnoid and brain tissue in this region which was removed had scar tissue formation extend through it.

Examination on December 9, 1954, revealed slight weakness of the right leg which was clumsy. The right patellar and Achilles reflexes were increased and a right Babinski sign was present. No convulsions had occurred after surgery. Follow-up examination on March 22, 1955, indicated that the child had gained 5 lb. and was more vigorous. He had had no seizures. He is taking ¾ gr. of phenobarbital twice a day.

Case 2. L.J., a 10-year-old white male had his first convulsion at the age of 8 years. He had a moderate head injury at the age of 7 years and otherwise had always been well. He had 1 convulsion each week which began with dizziness and loss of visual imagery of the right upper extremity. The right arm then became numb and began to jerk without the right leg being disturbed. Phenobarbital could not control the attacks. Examination disclosed weakness of the muscles of the right side of the face and right arm. There was atrophy of the right arm believed possibly due to poliomyelitis. He was left-handed. The reflexes of the right arm were increased, and the right arm was ataxic. He had right Hoffmann and Babinski signs. Electroencephalogram on November 9, 1950, showed a left centroparieto-occipital focus. Electroencephalogram on November 14 revealed a spike and slow wave pattern everywhere but mostly in the left temporoparietal area. Pneumoencephalogram on November 11 was normal. Craniotomy was done on December 1, 1950. The electrocorticogram demonstrated abnormal changes in the left parieto-occipital area. The area of epileptogenic cortex was excised. The tissue appeared to be involved with gliosis. No tumor cells were found in the tissue.

Electroencephalogram on December 11, 1950, showed diffuse paroxysmal dysrhythmia with less evidence of focal abnormality than seen before.

Electroencephalogram on February 12, 1953, disclosed pronounced improvement over the previous records but was still somewhat abnormal.

Follow-up on March 21, 1955, indicated that the patient was getting along well and did not take any medication. No convulsions had occurred after the operation. His right arm seemed somewhat weaker than the left but was not clumsy.

Case 3. J.R.B., a 12-year-old white male, began to have convulsions at the age of 9 years. He had bulbar poliomyelitis at 5 years of age associated with periods of cyanosis. This condition was believed to be responsible for the brain damage and eventual epilepsy. He had measles, mumps, and chickenpox at a younger age. Mild rheumatic fever occurred at 7 years of age, and he suffered a mild head injury when he was 12 years old. During the convulsions, he tried to climb walls, trot about, lie on the floor, or arise from his seat in the school room and open and close doors. He never had knowledge of these episodes of automatism. These attacks often lasted two or three minutes at a time and

then were repeated over and over again. He never had grand mal attacks. Mebaral and phenobarbital had failed to control these attacks.

He seemed to have normal intelligence. Physical and neurologic examinations were normal. Electroencephalogram on November 19, 1951, was abnormal with slow waves and random spiking in the right frontal and temporal regions. Electroencephalogram on September 29, 1953, showed a lesion in the right frontotemporal area with psychomotor and grand mal manifestations. Pneumoencephalogram on October 3, 1953, demonstrated normal subarachnoid spaces and the right lateral ventricle was slightly larger than the left.

Electroencephalogram on November 17, 1953, demonstrated slow waves of high voltage over the anterior half of the right temporal lobe and inferior surface of the right frontal lobe.

Craniotomy was done on November 18, 1953. Electrocorticogram localized the abnormality in the inferior gyrus of the right frontal lobe and in the anterior right temporal lobe. These areas were removed and the tissue disclosed diffuse perivascular scarring.

He improved and had no seizures until one month postoperatively. Then episodes of mental blankness developed, during which time he stamped his feet and pounded his hands. At such times, he became ashen white. Episodes of automatism did not occur. He was treated with phenobarbital and Tridione.

Electroencephalogram on August 4, 1954, showed epileptogenic activity in the right frontal and temporal areas. Pneumoencephalogram on September 6 revealed only some right lateral ventricle enlargement. Craniotomy was repeated on August 30. Electrocorticogram failed to reveal any distinct abnormal cortical or subcortical readings. There were subdural fibrinous adhesions which were dense over the lower frontal area. These adhesions were separated from the brain surface. This scarring was believed to be epileptogenic. Guttapercha membrane was left between the dura and brain surface until the third postoperative day. Pneumoencephalography was done on September 6 to introduce air into the subdural and subarachnoid spaces to try to prevent adhesions. Cortisone was given postoperatively, also with the same rationale.

His convalescence was satisfactory. He developed a few daily petit mal seizures after September 20, 1954, but was much improved otherwise. He was maintained on Dilantin and phenobarbital medications.

Follow-up information on March 22, 1955, revealed that he had 6 to 8 petit mal seizures during a day and then did not have a recurrence for two or three days.

He was examined last on April 8, 1955. Mysoline had been discontinued one week previously when he was placed on triple bromides and a ketogenic diet. No seizures have recurred during this treatment. Physical and neurologic examinations are normal. Another electroencephalogram will be needed and if this is localizing and his attacks recur, further cerebral surgery may be required.

Case 4. J.K., a 12-year-old white female, had a normal birth, but sudden left hemiplegia developed at 8 months of age. Convulsions began at 2 years of age, and fainting spells developed at 5 years of age. She had several episodes of status epilepticus. She had measles, whooping cough, and scarlet fever during childhood.

The convulsions had no aura. Jerking movements involved the left arm and face. She bit her gums. At times the left arm was weak after a seizure. Examination on June 28, 1952, revealed a prominent metopic cranial suture. Slight paresis and atrophy of left arm and leg were present. The left leg was ataxic. There was slight left facial paresis. Very little reflex difference existed.

Electroencephalogram on March 11, 1952, was abnormal. There was a large persistent build-up and diffuse 3 to 4 bursts of slow activity per second. This represented a grand mal type of epilepsy.

Electroencephalogram on July 10, 1952, demonstrated maximum frequency and potential in the right temporoparietal area which indicated this as the focus. Electroencephalogram on July 11 was a sleep recording and localized the epileptogenic focus in the right temporal area. Various forms of drugs including chloral hydrate had been unsuccessful in controlling the seizures. Skull roentgenogram on June 30 was normal. Pneumoencephalogram on July 1 revealed absence of the septum pellucidum and agenesia of the corpus callosum. There was one common chamber for the anterior horns of the lateral ventricle and the third ventricle.

Craniotomy was performed July 24. Electrocorticogram demonstrated an area 2 by 3 in. over the motor cortex for the leg and trunk that functioned abnormally. This cortex which was scarred with gliosis was excised. The remaining exposed cortex was normal. Good postoperative convalescence followed. There was slight weakness and numbness of the left side of the face and the left arm and leg. Dilantin and Mebaral were given after the operation.

Psychometric tests during follow-up revealed a dull normal intellect. Her grades have been fair. She has had a few convulsions but is much improved.

Follow-up information of April 21, 1955, indicated that she was getting along fairly satisfactorily in the ninth grade in school, although her learning ability and performance are slow. Her left arm was somewhat weak and ataxic, but the left leg functioned well. She had occasional headaches. She takes Dilantin and Mebaral daily and has had about 1 petit mal attack each week.

Case 5. J.S., a 17-year-old white male, was believed to have had a birth injury and convulsions began at the age of 3 years. Major seizures occurred about once each week with unconsciousness. There was no aura. Unconsciousness lasted about one minute. Jerking movements began in the left arm. Status epilepticus occurred at the age of 5 years with 22 minor attacks. Ketogenic diet, phenobarbital, and Dilantin were used in an attempt to control the attacks. Pneumoencephalogram was normal in 1942. Electroencephalogram on July 7, 1948, demonstrated a right temporal focus.

He left school in December, 1951, in the eleventh grade. Physical and neurologic examinations were normal. Electroencephalogram on February 28, 1952, revealed a right temporal spike focus. Pneumoencephalogram on March 25 was normal.

Craniotomy was done April 9. Electrocorticogram indicated a high voltage, slow waves and random spikes in a 1½ in. square area along the tip of the right temporal lobe and lower part of the posterior aspect of the rolandic fissure. The cortex and the white and scarred tissue in a 2 by 4 in. area were excised. Electroencephalogram on April 18 demonstrated many random spikes and random slow waves in the right temporoparietal area. His convalescence was good. He was placed on phenobarbital and Dilantin medications.

Examination on April 15, 1954, was normal. He finished high school in June 1954. No anticonvulsant medication has been taken since September 1954. No convulsions occurred after the operation. He is somewhat uncooperative and obstinate but well physically.

Follow-up on March 26, 1955, disclosed that he has

had no convulsions since the operation and does not take any medication. He is stubborn and independent but is getting along well at the present time.

Case 6. J.U. is a 26-year-old white female in whom right ear infection developed during childhood with drainage and eventual chronic mastoiditis. In 1931, at the age of 4 years, she had a right mastoidectomy. Major convulsions developed at the age of 9 or 10 years with periods of unconsciousness and clonic movements. Skull roentgenograms in 1941 and 1942 showed calcification in the right temporal cerebral lobe. Physical and neurologic examinations were normal.

She developed episodes of rage in 1943. Antagonistic behavior began in 1946 and institutional care became necessary. Electroshock treatment was used. In 1946, 75 to 90 per cent of her conversation was estimated to be normal. Three electroencephalogram examinations showed typical waves of psychomotor epilepsy localized in the right temporal lobe. Skull roentgenogram revealed an area of calcification 1 cm. in diameter in the right temporal lobe.

Pneumoencephalogram on January 8, 1953, was normal. Craniotomy was done on February 3, 1954. Electrocorticogram was indefinite, but monopolar depth electrode readings in the midpart of the right temporal lobe from 2 to 5 cm. showed abnormal spiking. The right temporal lobe containing the calcified and degenerated granulomatous area of tissue 1.5 cm. in diameter was excised. Postoperative recovery was satisfactory. She was given 1 gr. of phenobarbital every six hours at first.

Follow-up on March 30, 1955, disclosed that she is making better adjustments during the longer and more frequent visits home from the psychiatric hospital. She had had no convulsions since the surgery. No temper rages had occurred for several months. She had not received any medication for the past four to five months. She had become progressively more receptive and cooperative, and her return to society was anticipated.

Case 7. V.J. was a 32-year-old white female in whom in 1931, at the age of 9 years, right mastoiditis developed, and a mastoidectomy was performed. In 1932 a right temporal lobe brain abscess developed which was drained. The convalescence was complicated by unconsciousness and convulsions. After 1937 many of the convulsive attacks occurred without unconsciousness until after pregnancy in 1946 when the convulsions were represented by unconsciousness and clonic and tonic phases. Right temporal headaches developed, and she began to have 2 attacks daily. The aura of an attack began to have fantastic and horrible dream content, often concerned with destroying her son.

Medications such as phenobarbital, Benzedrine, Dilantin, and Mesantoin failed to control her epilepsy. Physical and neurologic examinations were normal. Pneumoencephalogram on July 2, 1952, showed some enlargement of the ventricles and the subarachnoid spaces indicative of some diffuse cerebral atrophy. There was rarefaction of the right temporal bone. Electroencephalogram on July 7, 1952, revealed spiking waves in the right temporal area which served as the epileptogenic focus. Electroencephalogram on May 26, 1954, showed spikes and slow high voltage activity over the right anterior temporal area. Craniotomy was performed on June 2, 1954. The electrocorticogram demonstrated abnormal waves over the right temporal lobe. About two-thirds of the entire right temporal lobe was removed. Dense scar tissue formation was found throughout this excised tissue. Postoperative convalescence was complicated by some periods of mental blankness and masticatory attacks on the left side. She improved and returned to her work as a nurse and homemaker.

On July 18, 1954, when attending a funeral, the first seizure after leaving the hospital occurred. After October 9, 1954, she began to have 1 attack a week which consisted of some left facial twitching, movements of the left hand with incoordination of the left hand, and numbness of the left face, arm, and leg. No mental blankness nor unconsciousness occurred. She used phenobarbital.

Electroencephalogram on January 4, 1955, was normal. Follow-up on January 15 revealed that she felt well. She was advised to give up her many activities away from home and was placed on Mysoline medication. In April 1955 occasional short episodes of left face and arm twitching occurred, but in other respects she was quite well.

SUMMARY

Obviously, surgical treatment of certain types of epilepsy is effective. Careful diagnostic studies are required for selection of the suitable cases. Convulsive disorders should be detected in childhood so that proper therapy may be instituted before brain damage occurs.

DR. HENRY L. BOCKUS TO DELIVER THE JOURNAL-LANCET LECTURE "Mechanism of Abdominal Pain" will be the title of the thirteenth annual JOURNAL-LANCET Lecture to be delivered by Dr. Henry L. Bockus of Philadelphia. The lecture will be given December 1 at 8:15 p.m. in the Mayo Memorial Auditorium, University of Minnesota Medical Center. His discussion of this subject is authoritative and of interest to both the specialist and the general practitioner.

Dr. Bockus, a 1917 graduate of Jefferson Medical College of Philadelphia, is professor of medicine and chairman of the department of medicine at the University of Pennsylvania Graduate School of Medicine. He is an outstanding teacher and each year conducts a postgraduate course in Gastroenterology in Philadelphia.

While in Minneapolis, Dr. Bockus will participate in the postgraduate course in Gastroenterology to be held at the University of Minnesota December 1 to 3. His book "Gastroenterology" is one of the best written on this subject, and his remarks in this field are always well worth hearing.

Concept of Renal Tubular Insufficiency with Description of 3 Typical Cases

HOWARD G. WORTHEN, M.D., and ROBERT A. GOOD, M.D.
Minneapolis, Minnesota

Only recently has selective renal tubular hypofunction been recognized to be the basis for human metabolic disease. Fanconi[1] first suggested that malfunction of the renal tubules might cause rickets and separated rickets due to primary tubular disease from both classical rickets based on vitamin deficiency and typical renal rickets associated with failure of phosphorus excretion. He reasoned that the syndrome featured by hypophosphatemic vitamin D resistant rickets, aminoaciduria, glucosuria, and organicaciduria reflects failure of the renal tubules to reabsorb phosphorus, glucose, and amino acids from the ultrafiltrate of plasma. Fanconi's syndrome, therefore, was the first disease attributed clearly to failure of renal tubular mechanisms.

Lightwood[2] and Butler and associates[3] described another syndrome which they related directly to renal tubular inadequacy. This disturbance, metabolically characterized by the existence of hyperchloremic acidosis, develops because the renal tubules cannot conserve fixed base. The Fanconi and Butler-Lightwood syndromes along with several other closely related diseases have been extensively studied in recent years and much has been learned of their etiology and pathogenesis.

Investigations carried out to date support the hypothesis that selective renal tubular insufficiency may be the basis for human disease and justify grouping several apparently unrelated syndromes together as disorders reflecting an underlying renal tubular inadequacy. Further impetus to the study of renal tubular disorders was provided by Dent[4] who first used paper chomatography to reveal abnormalities in urinary excretion of amino acids. Discovery of the occurrence of aminoaciduria in a number of conditions followed. Recently Dent,[5] Jackson and Linder,[6] as well as Fanconi[7] have amplified the concept of renal tubular insufficiency and have attempted to classify tubular disturbances on the basis of the metabolite which is mishandled.

The purpose of this report is to restate the concept of renal tubular insufficiency, to describe the diseases presently attributed to this form of metabolic failure, and to illustrate its role in the pathogenesis of human disease by presenting 3 cases recently studied in our laboratory whose illness was based on inadequacy of renal tubular function.

The renal tubule has the following major activities:

1. Excretion of nitrogenous wastes.
2. Reabsorption of important nutritional components from the ultrafiltrate of plasma. The latter include primarily glucose and amino acids.
3. Regulation of acid-base composition of the body fluids. This regulation is achieved by reabsorption of anions and cations in varying proportions, by formation of an acid urine and by secretion of ammonia to protect the fixed base reserves of the body.
4. Regulation of the osmotic pressure of the body fluids by reabsorption of water. The latter in turn is a function of the amount of available water, the amount of water necessary to meet the solute demand, the availability of antidiuretic hormone and responsiveness of the kidney to the latter compound.

Although not completely established, present evidence suggests that specialization of functions exists in the different sections of the renal tubule. For example, the proximal portion appears to be responsible for reabsorption of the greatest share of the glucose and amino acids, as well as most of the electrolyte and some of the water. The distal tubule actively regulates acid-base balance and controls osmotic pressure. It appears to be in the distal portion of the tubule that an acid urine is formed and that ammonium ions are substituted for requisite cations which are then returned to the plasma. Disorders of proximal tubular function appear to produce difficulties due to loss of essential metabolites, while distal tubular disorders result in abnormalities of acid-base and water equilibria.

Tubular damage accompanies most types of nephritis, but in generalized kidney disease the tubular disorder is generally overshadowed by glomerular malfunction. In most instances of

Read at the Pediatric Grand Reunion honoring Dr. McQuarrie on his 25th year of service to the University of Minnesota.

nephritis, glomerular damage is sufficient to permit only small amounts of glomerular filtrate to reach the tubules. As a consequence, even though many tubules are injured, sufficient tubular function remains to prevent expression of underlying tubular disease. The term tubular insufficiency, then, is generally restricted to clinical syndromes in which tubular insufficiency occurs in the absence of demonstrable glomerular damage or under circumstances in which the expression of tubular malfunction is the predominant feature.

The use of clearance technics permits relatively precise evaluation of glomerular and tubular function. Both functions can be measured with reasonable accuracy by methods now generally available. Thus, correcting for the rate of glomerular filtration permits the tubular function of one patient to be compared to that of another, in spite of differences in glomerular function. Consequently tubular disorders can be roughly quantitated.

Recently, 3 patients having renal tubular insufficiency have been studied in our laboratory. In each of these patients, renal function was studied by the use of standard technics for measuring renal clearance. These studies represent an attempt to delineate in these patients the nature and magnitude of tubular disease with maximum accuracy. Of these patients, 1 suffered from classical De Toni-Fanconi syndrome with cystinosis (Lignac's disease). The other 2 were examples of the disease first reported by Lowe and associates,[8] and more recently termed the oculo-cerebro-renal syndrome by Fanconi.[7]

CASE REPORTS

Case 1.[9] A white male child who was first seen at the University of Minnesota hospitals when 7 months of age, and who has been followed in our clinic to his present age of 3½ years. A brother 2 years older had typical Fanconi syndrome and cystinosis from which he died when 3 years of age.

The diagnosis of the Fanconi syndrome was made when this child was 7 months of age. The basis for the diagnosis was the occurrence of vitamin D resistant, hypophosphatemic rickets, renal glycosuria, renal aminoaciduria, organic aciduria, and metabolic acidosis. The diagnosis of cystinosis was made by demonstration of cystine crystals on slit lamp examination of the cornea, and upon microscopic study of the bone marrow aspirates.

Renal function studies were performed on this patient when he was 3 years of age. The results of these studies are summarized in table 1. Whereas the glomerular filtration rate was only moderately reduced, all of the tubular functions studied were markedly impaired.

The high rate of clearance of glucose and amino acids at normal plasma levels demonstrates clearly that the glycosuria and aminoaciduria have a renal basis.

The phosphaturia noted in Table 1 was reduced one-third by treatment with 100,000 units of vitamin D daily for three weeks, suggesting that the phosphaturia is at least partially due to secondary hyperparathyroidism.

The renal bicarbonate excretion was also high in this patient, and fell less than the normal amount when ammonium chloride was given. The ammonia excretion was normal or only slightly increased during a period of spontaneous acidosis, and rose only to the lower limits of normal with the induction of severe acidosis using ammonium chloride. The latter response was deemed inadequate and interpreted as a reflection of failure of the tubules to meet the demands of acidosis by the production of ammonia.

Case 2. A white male infant was admitted to the University of Minnesota hospitals for the first time at 1 month of age because of unexplained fever, weight loss, and dehydration. The unexplained fever continued throughout the patient's entire life but, after initial control, frank clinical dehydration was not again a problem.

Examination of the eyes revealed posterior polar cataracts bilaterally, as a consequence of which the child was virtually blind. Clinical observation revealed the almost constant presence of searching nystagmus. No demonstrable visual improvement was produced by needling of these congenital cataracts.

The child was obese, had flabby musculature and hyperextensible joints and appeared to be generally hypotonic. Study during the two and one-half years of observation revealed clear evidence of severe mental inadequacy. At no time did the child hold his head up, sit up, vocalize, or show interest in his surroundings. Even taking the visual impairment into account, profound mental retardation could be firmly established on the basis of the failure of sequential motor development. Repeated examination

TABLE 1

	CASE 1			CASE 2			CASE 3		
	Observed	*Per 1.73 m²*	*Ratio to normal*	*Observed*	*Per 1.73 m²*	*Ratio to normal*	*Observed*	*Per 1.73 m²*	*Ratio to normal*
Inulin clearance cc./min.	31	98	.8	28	88	.73	16.4	76	.63
PAH clearance cc./min.	78.3	250	.39	87.5	303	.50	31.2	142	.24
-amino N. clearance cc./min.	5.7	18	9.0	2.5	8.75	4.3	1.8	8.25	4.2
Glucose clearance cc./min.	10.6	33.4							
Phosphorus clearance cc./min.	9.8	30.9	2.5						
TM PAH (mg./min.)	8.7	28	.36	12.14	42	.55	6.6	30	.39
Filtration fraction	.4		2.0	.32		1.6	.53		2.6
c -amino N/Cin	.22		10.0	.089		4.5	.11		5.0

of the urine revealed constant albuminuria and occasional glycosuria. Blood chemistries showed hyperchloremic acidosis, hypophosphatemia, normal serum calcium, and an elevated alkaline phosphatase. Repeated study of twenty-four-hour urine collections demonstrated a constant aminoaciduria and organic aciduria. In this patient, glycosuria was never quantitatively significant. Upon administration of ammonium chloride, the response of urinary titratable acidity and production of ammonia were much less than is normally to be expected in the face of this challenge to tubular function.

Examination of the cornea and bone marrow revealed no evidence of deposition of cystine crystals, nor did biopsy of the liver, lymph node, and kidney show evidence of cystinosis. The glycogen content of the liver as studied by histochemical methods was interpreted as being normal.

Case 3. The younger brother of case 2 demonstrated nearly identical symptoms, physical findings, and chemical changes as those observed in his sibling. However, this patient had glaucoma of the left eye which required an Elliot trephination for correction. This patient likewise had albuminuria, occasional hypophosphatemia, elevated alkaline phosphatase, and hyperchloremic acidosis.

The appearance of these siblings was strikingly similar. Both were fat with round faces and sunken eyes. Both were hypotonic with flabby, poorly developed muscles, and both showed athetosis of the arms and had high-pitched, piercing cries.

The renal function studies done on these patients are shown in table 1. In these children, as in the patient with classical Fanconi syndrome, tubular function is depressed far more than is glomerular activity.

The studies were done in these patients to determine whether the renal tubular anomaly might be the same as that in the patient with the Fanconi syndrome. Although of greater severity in the patient with Fanconi's syndrome, the basic anomaly seems to be similar in all 3 cases. In each instance we have demonstrated glomerulotubular imbalance and failure of absorption of certain solutes from the relatively excessive amount of glomerular filtrate. An important qualitative difference is the absence of significant glycosuria in the cases with Lowe's syndrome. In reality, however, the striking difference in the 2 tubular diseases is the far greater severity of tubular malfunction in the patient with Fanconi's syndrome. This patient was given extremely large amounts of sodium and potassium citrate (up to 500 mEq./m^2/day) without correction of the acidosis, and vitamin D had little effect on the rickets until a dose of 100,000 units daily was used. In the other cases, the acidosis and rickets could be controlled with 50 mEq./ of base/m^2/day and 2,500 to 5,000 units of vitamin D daily.

The explanation for the greater severity of the acidosis and its resistance to therapy in the patient with the Fanconi syndrome probably lies in impaired bicarbonate reabsorption. It is undoubtedly the wasting of fixed base as a function of the excessive loss of bicarbonate which accounted for the resistance of the acidosis to correction in this patient.

DISCUSSION

These 3 cases serve to emphasize both the similarities and the differences that occur in diseases based on malfunction of the renal tubules. Included in this group is a whole spectrum of anomalies ranging from mild, asymptomatic conditions to disorders associated with tubular insufficiency producing pronounced metabolic derangement and clinical disease.

The first representative of this group which we shall discuss is hereditary renal glycosuria. Hereditary renal glycosuria is a benign condition due to a reduced capacity of the renal tubules to absorb glucose. Patients having this condition are said to have a low renal "threshold" for glucose. The amount of sugar lost in the urine in this condition is generally insignificant compared to the amount ingested, and the spillage of glucose causes no difficulty. The condition, therefore, is ordinarily a laboratory disease without clinical expression. An occasional patient with this anomaly is erroneously diagnosed as having diabetes mellitus and placed on a curtailed carbohydrate intake. As a consequence, ketosis may ensue resulting in mild to moderately severe acidosis.[10]

Ketosis occurring under these circumstances is probably due to the development of hypoglycemia caused by loss of glucose in the urine without commensurate increase of glucose intake. Somogyi[11] has shown that hypoglycemia results in ketonemia by stimulating rapid hepatic glycogenolysis.

Hereditary cystinuria is another relatively benign condition which, however, is somewhat more troublesome than renal glycosuria. The physiologic abnormality, here again, is reduced reabsorptive capacity of the renal tubules. Instead of glucose, cystine, lysine, arginine, and sometimes ornithine are lost in the urine[12, 13] even though the blood levels for these amino acids are normal.[13] Thus we are dealing in this instance with a form of renal aminoaciduria. This condition may become symptomatic when the relatively insoluble amino acid, cystine, precipitates in the urinary tract and forms calculi which traumatize the mucosa or produce obstruction of the urinary tract with its many concomitants. The aminoaciduria associated with this form of renal anomaly is limited largely to the 4 amino acids, cystine, lysine, arginine and ornithine and may be termed a "segmental aminoaciduria."

Besides the relatively limited aminoaciduria occurring in hereditary cystine disease, general-

ized aminoaciduria has been noted to occur in several hereditary conditions. Wilson's disease[14,15] (hepatolenticular degeneration) and galactosemia[16] are both associated with aminoaciduria, involving a large number of amino acids. In both of these diseases an attractive hypothesis is that the aminoaciduria does not reflect an hereditary defect of the renal tubules but rather represents a function of renal toxicity of a metabolite being excreted in excessive quantities as a consequence of a basic metabolic disturbance. In Wilson's disease, for example, the accumulation and excretion of abnormal amounts of copper has been demonstrated, whereas in galactosemia large amounts of galactose are being excreted in the urine. In Wilson's disease, the copper dysmetabolism appears to be primary and most authors consider the aminoaciduria to be due to a noxious effect of copper on the renal tubules.[17] In galactosemia, removal of the presumed intoxicant results in decreased aminoaciduria, whereas its addition reinstates the aminoaciduria.[18–20]

Experimental and clinical evidence tends to support the concept that aminoaciduria may be secondary to tubular injury. It has been shown in both man and experimental animals, for instance, that aminoaciduria may result from poisoning with lead,[21] uranium,[22] nitrobenzene,[23] and cresol.[24] Supporting the concept that the aminoaciduria of galactosemia is not an inborn tubular anomaly is the fact that the aminoaciduria regularly disappears when galactosemia and galactosuria are eliminated by the use of a milk-free diet.[20]

Vitamin deficiency may also result in a secondary aminoaciduria. Clinical rickets, clinical scurvy, and experimental vitamin E deficiency in rabbits are accompanied by a generalized renal aminoaciduria which disappears promptly upon correction of the vitamin deficiency.

Another renal tubular disease is represented by "idiopathic hypercalcuria." [25] Here the failure of tubular reabsorption of calcium appears to be the only demonstrable defect. This condition may be followed by 2 complications and give rise to clinical disease. First, renal stones or renal calcification may form as a consequence of the high concentration of calcium in the urine. Second, demineralization of the bones with concomitant pain or fractures may result if absorption of calcium from the gastrointestinal tract does not keep pace with loss of calcium in the urine.

Another anomaly of tubular function possibly due to failure of reabsorption of phosphorus by the proximal convoluted tubule should be mentioned, although controversy exists as to the proper classification. This condition is vitamin-D-resistant rickets. Fanconi[7] and others[5,6] feel that this disease is based on an intrinsic renal tubular lesion resulting in deficient phosphate reabsorption which in turn leads to renal phosphaturia and hypophosphatemia. Fanconi uses the term "phosphate diabetes" to describe this condition which he attributes to a specific tubular defect. However, the evidence favoring this view is not sufficiently conclusive, and it remains a possibility that the phosphaturia reflects a secondary hyperparathyroidism such as that which occurs with ordinary vitamin D-deficient rickets rather than a primary tubular anomaly. For example, the phosphaturia of ordinary rickets may be as great as that found in resistant rickets. In the former, the phosphaturia is eliminated when the rickets has been corrected by administration of vitamin D. Until it has been demonstrated that patients with resistant rickets continue to exhibit phosphaturia after the rickets have been corrected by administration of vitamin D, the existence of a specific tubular lesion must be questioned. In support of the Fanconi hypothesis is the observation of low serum phosphorus levels following complete chemical and roentgenologic healing of the rickets.[26]

Tubular insufficiency may be limited to distal tubular functions. As previously mentioned, the distal tubule has the responsibility for regulating concentration of the urine by reabsorbing water needed by the body. If the cells of the distal tubule fail in this capacity, nephrogenic diabetes insipidus results. The polyuria of nephrogenic diabetes insipidus is clinically similar to the form of diabetes insipidus due to pituitary or hypothalamic disease resulting in lack of antidiuretic hormone. The renal form of diabetes insipidus, however, is not affected by Pitressin since the end organ response is deficient. In this disease, the urine volume is determined by the amount of solute the kidney must excrete. When the solute load is high, the urine volume is high. When the solute load is reduced, the urine volume falls but remains excessive. The only therapy found which will reduce the urinary volume is dietary restriction which decreases the obligatory solute load on the kidneys. This disease appears to be hereditary and may express itself clinically early in infancy. The defect appears to be due to a deficiency in water retaining function of the convoluted tubules since the other distal tubular activities are intact in these patients. Further than this the pathogenesis of nephrogenic diabetes insipidus has not been established. The syndrome is presumed to be due either to absence of normal mechanisms for reabsorbing water against a concentration gradi-

ent or resistance of these mechanisms to activation by the antidiuretic hormone from the pituitary. These patients often die in infancy although, in a few instances, evidence of a self-limited form of the disease has been presented.

The production of hydrogen and ammonium ions by the kidney constitutes the homeostatic basis for maintenance of the normal acid-base balance of the blood and body water. Excretion of hydrogen and ammonium ions permits reabsorption of an equivalent number of cations, (sodium, calcium, potassium) and results in the excretion of a larger number of *filtered* anions than *filtered* cations. The consequence of this adjustment in the normal person is the production of an acid urine and the conservation of fixed base. Failure of the mechanisms responsible for exchanging hydrogen ions for sodium ions or of the mechanisms for ammonia production may result in loss of fixed base and a systemic acidosis. Hyperchloremic metabolic acidosis, which occurs when these tubular functions are deficient, has been termed the Lightwood-Butler-Albright syndrome. Albright and Reifenstein,[27] Doxiadis,[28] Latner and Burnard,[29] and Lightwood and associates[30] have discussed the pathogenesis of this disorder in detail and have attempted to classify its subdivisions.

An apparently identical metabolic disorder has been produced experimentally in both man and animals by the administration of the carbonic anhydrase inhibitor 6063 (Diamox).[31] This observation has been interpreted as evidence that the Lightwood-Butler-Albright syndrome may be due to deficiency or absence of carbonic anhydrase activity in the kidney. Carbonic anhydrase increases markedly the rate of conversion of carbon dioxide to carbonic acid. As a result of this process, metabolic carbon dioxide can supply hydrogen ions for excretion in the kidneys. This conversion permits reabsorption of a corresponding amount of fixed base, for example, sodium ion. The bicarbonate ion produced in the carbonic anhydrase reaction supplies the companion ion necessary to maintain electrical neutrality during the reabsorption of the sodium ion or other base.

Administration of Diamox, the carbonic anhydrase inhibitor, interferes with the exchange of hydrogen ion for cations in the renal tubule. Thus, this form of treatment markedly increases excretion of both sodium ion and bicarbonate ion indicating failure of the acidification process and its attendant base-sparing result.

Further, excretion of ammonium ion by the renal tubule is, in part, a function of pH of the tubular urine. This is due to a decreased rate of transport of ammonium ion into a urine of relatively high pH. It has been observed that administration of Diamox results in increased loss of base and bicarbonate as well as decreased excretion of ammonium ion. When Diamox has been given, an increased excretion of bicarbonate is readily demonstrated and quantitative data indicate that approximately 40 to 50 per cent of filtered bicarbonate is lost in the urine under these circumstances. Normally, a very small amount of the filtered bicarbonate is thus excreted. These data suggest to Berliner[32] that most bicarbonate reabsorption is a function of hydrogen ion exchange. Berliner's observations suggest further that the deficiency of carbonic anhydrase activity may exist throughout the entire length of the tubule rather than in the distal segment alone. For this reason he proposes that the Lightwood-Butler-Albright syndrome cannot be considered to be a disorder of the distal tubule alone. The hypopotassemia which occurs in the Lightwood-Butler-Albright syndrome and occasionally results in clinical symptoms in these patients could well be due to depression of renal carbonic anhydrase activity. Potassium secretion appears to be a function of a process which competes with hydrogen ion secretion. If hydrogen ion secretion is deficient, potassium secretion is accelerated and hypopotassemia may result. Potassium loss by this mechanism may be progressive and become clinically significant unless the intake of potassium is increased.

The Fanconi syndrome is not only the first described, but also the prime example of renal tubular disease. Not one, not a few, but many tubular functions appear to be involved in patients suffering from this disorder. The tubules of these patients fail to reabsorb the normal amounts of glucose, amino acid, phosphorus, or bicarbonate from the ultrafiltrate of plasma.

The renal glycosuria and aminoaciduria are presumed to be due to defects in the enzyme systems of the proximal tubular segment and are thought to be similar to the deficiencies that exist in the several other types of renal glycosuria and aminoaciduria described above. The phosphaturia may be due to a specific defect of the tubules resulting in failure of adequate phosphate resorption even in the presence of a low serum phosphorus concentration. The fact that phosphaturia responds, in part at least, to treatment with vitamin D and supplementary base[33] suggests that it may be due partly to hyperparathyroidism secondary to the chronic acidosis and wasting of fixed base. The increased bicarbonate clearance demonstrated in patients with Fanconi syndrome may, as is probably the case in the

Lightwood-Butler-Albright syndrome, be due to a deficiency in renal carbonic anhydrase activity. Excessive loss of potassium, which represents a real clinical danger in patients with Fanconi syndrome, likewise may be based on the increase in potassium secretion which accompanies deficient secretion of hydrogen ions in the renal tubules. Alternately it is possible that failure of potassium reabsorption in the proximal tubules accounts for excessive loss of this metabolically important ion. The organicaciduria which is a regular laboratory concomitant of De Toni-Fanconi syndrome may also be based on deficient reabsorption of organic acids from the glomerular filtrate due to tubular malfunction of another type. However, the frequently positive acetonuria in these patients may signify that organicaciduria is here, to some extent at least, due to ketonemia occurring as a consequence of the renal glycosuria. Simultaneous quantitation of ketone body concentration in the blood and organic acid excretion in the urine, which to our knowledge has not yet been done, would clarify this point.

In addition to the reabsorptive defects of the proximal tubules, patients with Fanconi syndrome appear to have secretory inadequacies clearly demonstrated in the reduction of the clearance and maximum excretory capacity for para-aminohippuric acid. Although the secretory deficiencies may play little role in the clinical disease of these patients, they serve to emphasize the general nature of the proximal tubular disturbance. These observations support the concept that involvement of one or few enzyme systems probably cannot explain the entire metabolic disturbance in Fanconi syndrome even though such may be the case in some of the other tubular malfunctions mentioned above. In the Fanconi syndrome either multiple enzyme systems are involved or there is a generalized reduction of function of the entire renal tubule.

The finding of Clay and associates[34] that the proximal tubule is short and joined to the glomerulus by an abnormally narrow neck, suggests that an anatomic abnormality of the tubule may be responsible for all of the renal defects of renal function occurring in the Fanconi syndrome. Compatible with available data would be the hypothesis that a total reduction in proximal tubular area would result in an overt dysmetabolism of all those substances handled exclusively or principally by this morphologic unit.

Recently Harrison and Harrison[35] following a lead presented by Berliner and associates[36] discovered that the parenteral administration of maleic acid or maleate to rats produced a condition characterized by the development of renal glycosuria, renal aminoaciduria, and renal phosphaturia. Chromatographic studies revealed that the aminoaciduria induced in this way was featured by the excretion in the urine of the same amino acids which are excreted in excessive quantities in the urine of patients with the Fanconi syndrome. To this extent these workers have succeeded in producing an experimental model of the Fanconi syndrome. Although this discovery does not yet solve the problem of whether the Fanconi syndrome is the function of a disturbance of a single tubular mechanism or whether multiple homeostatic regulators are disordered in this disease, it offers an opportunity to approach these questions through an incisive experimental model. Preliminary data reported by Harrison and Harrison indicate that the metabolic derangement of the "experimental maleate induced Fanconi syndrome" cannot be corrected by even massive doses of vitamin D.

In a paper recently presented by Salassa and associates,[37] evidence was submitted suggesting that not only the phosphaturia, but the glycosuria and aminoaciduria of the Fanconi syndrome in man respond to therapy with massive doses of vitamin D. Although the data presented in this study are impressive for the particular case treated, they are in confliet with the observations of others[6] and experiences in our laboratory indicate that generalization from this experience to all cases of Fanconi syndrome cannot be made. Each of 2 cases of Fanconi syndrome which we have studied intensively[9] were treated with massive doses of vitamin D until the rickets healed and vitamin D intoxication ensued. In spite of this therapy, aminoaciduria, glucosuria, and wastage of base persisted unchanged in 1 patient and the reduction of aminoaciduria in the other was at least in part explained by evidence of rapid glomerular failure during vitamin D therapy and only partly a result of improvement in tubular function. The one feature of Fanconi syndrome which remains completely enigmatic is the progressive nature of the disease. The most attractive possibility seems to be that progress here is a function of a vicious cycle induced by deposition of cystine or other toxic materials in the tubular cells and interstitial tissues of the kidney with the progressive development of interstitial fibrosis, glomerular malfunction, and tubular destruction. Since the blood concentration of cystine as well as other amino acids is not high in Fanconi syndrome, the basis for cystine deposition remains obscure.

Although from recent studies much has been learned of the nature of Fanconi syndrome, and

the other tubular disorders discussed in this paper, much still is unknown. Completely satisfactory medical management of the clinical diseases based on these tubular disturbances in many instances awaits further basic research.

SUMMARY

1. The concept of renal tubular insufficiency is restated.

2. Three representative cases of renal tubular disease are presented. These cases include 1 patient with typical De Toni-Fanconi syndrome and cystinosis and 2 cases representing oculo-cerebral-renal syndrome of Lowe.

3. The results of renal clearance studies on these patients are presented.

4. Each of the separate known clinical entities based on renal tubular insufficiency is discussed from the standpoint of the pathologic physiology and the underlying mechanisms involved.

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Guillain-Barré Syndrome

Report of 2 Cases Treated with Cortisone

PAUL J. BRESLICH, M.D.
Minot, North Dakota

In 1916, Guillain, Barré, and Strohl[1] described a radiculoneuritis in which examination of the spinal fluid disclosed a pronounced increase of the spinal fluid protein with no abnormal increase of the cell count. This symptom complex had apparently been recognized by many authors under different diagnostic designations for more than fifty years. Pullen and Sodeman,[2] in 1946, listed 23 distinct names under which the disease had been reported, including Landry's ascending paralysis, which was described in 1859. While there is no universal agreement that the case reported by Landry belongs in this group, Haymaker and Kernohan[3] in a detailed study of the subject in 1949 entitled their paper the "Landry-Guillain-Barré syndrome." To avoid further confusion in diagnosis and terminology, most authors are content to refer to the disorder as the Guillain-Barré syndrome until such time as the pathogenesis of the illness is finally explained.

The symptoms in most instances appear a few days or weeks after the patient has suffered a mild infectious illness, often an acute upper respiratory infection or a gastroenteritis or after many of the well-known bacterial or viral infections. Men are apparently affected more often than women and while patients of all ages may suffer from the syndrome, reports appear with the greatest frequency in the group between 20 and 50 years of age. Sensory disturbances, such as numbness in the feet or hands, precede motor disturbances in about one-half the cases, but occasionally paralysis of the extremities or of the muscles supplied by the cranial nerves may be the first sign. Perception of touch is usually only slightly diminished, but the loss of sensation may progress to complete anesthesia. Changes in motor function may vary from weakness of the limbs to almost complete paralysis. Weakness usually begins in the legs and may ascend to involve the arms and finally the cranial nerves, of which the facial nerves are affected in about one-third of the cases. Although paralysis of the facial muscles occurs with greatest frequency, diseases of other cranial nerves may cause disturbances of swallowing, phonation, vision, and hearing. Paralysis of the intercostal muscles and of the diaphragm is of the utmost gravity and accounts for most of the deaths. Fox and O'Connor[4] found a death rate of 20 per cent in 126 cases which they reviewed, and Forster and associates[5] report a mortality of 42 per cent in 26 patients where death occurred in 11 of 13 cases where respiratory paralysis developed.

Some degree of fever is present in most patients but is seldom high except when complications such as pneumonia appear.

The neurologic examination usually shows some diminution in sensation over the involved extremities. The tendon reflexes disappear and the Babinski reactions are normal or absent. The abdominal reflexes diminish as the illness progresses. In severe cases, the limbs are flaccid with almost no evidence of voluntary movement. Weakness of the facial muscles may be most pronounced on one side of the face but is often bilateral.

Recovery sometimes occurs with dramatic suddenness or may require two or three months. Many patients show evidence of residual paralysis after several years. Improvement often takes place in the reverse order in which the paralysis appeared.

The laboratory tests most helpful in establishing the diagnosis concern the spinal fluid, which when obtained is clear and colorless and under normal or slightly increased pressure. The cell count is normal or occasionally slightly elevated and the cells are entirely of the lymphocyte series. The spinal fluid protein is markedly elevated in most instances. Early in the disease, it may be normal or only slightly elevated, but later it may reach very high levels with no increase in the cell count. Values of 160 mg. per cent to 300 mg. per cent are most often recorded,

PAUL J. BRESLICH, *a 1928 graduate of Rush Medical College, is with the department of internal medicine at the Northwest Clinic, pathologist at Trinity Hospital, and consultant in internal medicine at Veterans Administration Hospital, all in Minot, North Dakota.*

but they may be much higher. Changes in the spinal fluid sugar and chlorides are not significant, and no characteristic change in the colloidal gold curve occurs.

Examination of the brain and spinal cord at autopsy discloses no constant changes, but microscopic studies of the tissues show characteristic abnormalities which have been described in the reports by Roseman and Aring,[6] Scheinker,[7] and Haymaker and Kernohan.[3]

The most common finding is edema of the cranial and spinal nerves with occasional moderate increase in round cells and hyperemia. In addition, swelling and beading of the myelin sheaths occur and swelling, beading, and occasionally fragmentation of the axis cylinders. These changes are particularly pronounced in the spinal nerve roots. Changes of the neurons in the central nervous system may be widespread but resemble a reaction to injury of the peripheral nerves and are apparently reversible. Swelling and beading of the myelin sheaths and degenerative changes of the axis cylinders may also be found in the longitudinal nerve tracts of the spinal cord.

Scheinker suggested that the pronounced edema of the spinal nerve roots within the dural sheaths which cover the roots may actually result in strangulation of the nerves where they penetrate the meninges with consequent loss of function of the nerves. He accounted for the high incidence of facial weakness in the Guillain-Barré syndrome by the swelling of the seventh nerve within its long bone canal. Blockade of the perineural lymph spaces by edema of the nerves prevents drainage of spinal fluid through these spaces, and apparently the stagnation of the spinal fluid is in some way responsible for the markedly elevated protein. Scheinker found that cerebrospinal fluid from the cisterna magna showed no great increase of protein in patients with the Guillain-Barré syndrome even though the values were greatly increased in fluid obtained from the lumbar sac. His explanation for these findings was that the normal drainage of fluid over the brain into the arachnoid villi was not impaired.

The pathologic changes in the nerve roots suggested an allergic process to many authors. Stillman and Ganong[8] speculated that a similarity might exist between the Guillain-Barré syndrome and other "allergic" disorders which follow infections such as rheumatic fever and, on this basis, decided to use ACTH and cortisone in the treatment of a severely ill patient whose condition had steadily grown worse. Remarkable improvement was evident several hours after treatment was begun, and it was suggested that the adrenal cortical steroids might have brought about prompt resolution of edema and congestion in the nerve roots, preventing further injury to the nerves by compression in the dural sheaths. According to this view, the speed of clinical recovery depends on the degree of nerve injury. Brief periods of axon compression are compatible with a prompt return of function, whereas nerves damaged by more prolonged periods of compression require more time for recovery. Newey and Lubin,[9] and Blood and associates[10] have reported single cases treated with ACTH with excellent response. Equally good results were also described by Drenick and Avol[11] in 2 cases treated with cortisone. Fiese and associates[12] observed a case of polyneuritis of the Guillain-Barré type complicating infectious mononucleosis which was successfully treated with cortisone, and finally Tupper and Foster[13] reported a single instance in which recovery followed the use of very large doses of cortisone. None of these authors has advanced the claim that ACTH or cortisone are specific remedies for the Guillain-Barré syndrome because the course of the illness is unpredictable and dramatic improvement may occur spontaneously. The report of Von Hagen and Baker[14] presents instances where rapid improvement was observed in critically ill patients who were treated by other means and without the use of ACTH or cortisone. Of their 23 patients, 8 required respirator care and only 2 died, which is an unusually low mortality record.

Within the past five months, 2 patients with the Guillain-Barré syndrome were cared for in Trinity Hospital, and cortisone was used in the treatment in each instance. In both cases, the disease was associated with severe respiratory muscle weakness so that mucus could not be coughed up from the air passages. Both patients required repeated tracheal aspirations. In the first instance, the use of cortisone was followed by prompt improvement while, in the second, the patient showed some improvement but finally died from respiratory failure and a complicating purulent bronchitis.

CASE REPORTS

Case 1. A 45-year-old male white school teacher was brought to the hospital by ambulance on September 18, 1954, during an epidemic of poliomyelitis. On September 10, 1954, he had become ill with fever associated with severe aching pains in the arms, back, and legs. Gradually his arms and legs became numb and on September 14 he noticed pronounced weakness in his legs. The day before admission to the hospital, the right side of his face became weak and he was unable to close the right eye. Weakness of the legs progressed until he was

unable to stand unsupported. He was extremely apprehensive about his condition. His temperature was 98°, pulse 72, and respiratory rate 16. The right side of his face was completely paralyzed. Strength in his hands and arms was normal, and he was able to raise himself to a sitting posture in bed but was unable to move the left leg. The tendon reflexes in the arms and right leg were normal and the abdominal reflexes were active. The Babinski sign on the right was normal. The tendon reflexes in the left leg were absent, and there was no Babinski reaction. Sensation to touch was diminished in the legs, but position sense in all 4 extremities was not impaired. Examination of the nose, throat, neck, heart, lungs, and abdomen was negative. The urinalysis was within normal limits. The red blood count was 6,750,000, the hemoglobin 18.6 gm., and the white blood count 10,500 with 52 per cent lymphocytes and 48 per cent mature polynuclear leukocytes. X-ray films of the skull, cervical and lumbar spine, pelvis, and chest were normal except for old compression fractures of the bodies of the fifth and sixth dorsal vertebrae. The electrocardiogram disclosed a sinus tachycardia and was otherwise normal. The spinal fluid was clear, colorless, and under normal pressure. It contained 2 lymphocytes and 3 red blood cells per cubic millimeter. The total protein was 350 mg. per cent, the sugar 112 mg. per cent, the chlorides 720 mg. per cent, and the gold chloride curve was normal.

Weakness was noticeable in the right leg on September 19, and on September 23 he was unable to move a muscle in either leg. Sensation in the legs was so diminished that he no longer felt the prick of hypodermic or intramuscular injection. He no longer was able to determine the position of his arms or legs without looking at them. As the day wore on the intercostal muscles became weak, and respiration was carried on chiefly with the diaphragm. At this time the musculature of the left side of the face was appreciably weak, and he was unable to move his arms. He could not cough up mucus from the trachea and was unable to swallow fluids. He was now given 25 mg. of cortisone every four hours, and tracheal aspirations were carried out at regular intervals which permitted him to breathe comfortably for several hours at a time. After the administration of cortisone was begun, the paralysis showed no further progression. On September 25, he was able to cough up some mucus and on the following day the last tracheal aspiration was performed. On September 28, the strength of the arms was improved and he could grasp objects with his hands. On September 30, evidence of returning muscular movement in the legs was noted and on October 22 he walked a few steps. When he left the hospital on November 9, 1954, he felt strong enough to be up and about most of the day. Some weakness of the right side of his face was still present. The dose of cortisone was gradually diminished as improvement progressed and the drug was finally stopped altogether after the patient returned to his home.

Case 2. A 37-year-old white housewife was admitted to the hospital on January 1, 1955, because of an illness which began on December 18, 1954, with aching pains in the muscles, slight sore throat, vomiting, and diarrhea. She improved for a time and felt well on December 25, 1954. She complained three days later of a backache between the shoulder blades which was so severe that she was unable to work. She was given codeine for this pain and again became nauseated and vomited repeatedly which she attributed to the medicine. Her tongue felt burned and she lost her sense of taste. The legs seemed cold and numb. These symptoms continued to grow worse and finally caused her to seek hospital care.

The temperature was 97°, the pulse 76, and the respirations 16. She was restless and apprehensive and the backache required morphine for relief. Examination of the head, neck, heart, lungs, and abdomen was negative. No abnormalities of function of the cranial nerves were found. The tendon reflexes of the extremities and the Babinski reactions were normal. The white blood count was 8,150, the red blood count 4,600,000, and the hemoglobin 13.1 gm. The differential white blood count was within normal limits. The urine examination was negative. X-ray studies of the chest, thoracic spine, gallbladder, stomach, and bowel were normal.

On the morning of January 4, 1955, she complained to the nurse of weakness of the legs. She was unable to walk to the bathroom without assistance. She staggered when she walked. Sensation to touch was diminished in the legs and pronounced weakness was present in both legs and the right arm. The biceps and triceps reflexes were absent from the right arm. The knee jerks, ankle jerks, and Babinski reflexes were absent from both legs. The spinal fluid was clear and under a pressure of 160 mm. It contained only 1 lymphocyte per cubic millimeter. The spinal fluid protein was 168 mg. per cent, the sugar 95 mg. per cent, and the chlorides 730 mg. per cent. The gold chloride curve was negative and the Wassermann reaction negative.

On January 4, 1955, cortisone was given in doses of 25 mg. every four hours after an initial dose of 50 mg. Weakness in the legs continued to increase until on January 8 she was just able to wriggle her feet. The strength of the arms also was diminished. On the afternoon of January 8, she complained of difficulty in swallowing and was unable to cough up mucus because of weakness of the intercostal muscles. Cortisone was now increased to 200 mg. per twenty-four hours by intramuscular injections. Tracheal aspirations were resorted to in order to keep the air passages clean. She was also given penicillin and streptomycin to ward off a possible aspiration pneumonia. On January 11, she felt somewhat better and was able to eat cereal and custard, although she continued to have trouble clearing the air passages of mucus. Voluntary movement of the arms and legs increased. That evening difficulty was experienced in introducing the tracheal catheter because of laryngeal edema and a tracheotomy was performed. This gave considerable relief, but six hours later she suddenly became cyanotic and died in thirty-five minutes and before she could be placed in a respirator.

The postmortem examination carried out about seven hours after death disclosed the recent tracheotomy wound with the tracheotomy tube in place. Above the level of the tracheotomy, the trachea and larynx were filled with a viscid cloudy mucus and below the tracheotomy, the air passages were empty as far as the secondary divisions of the main bronchi. The smaller bronchi were filled everywhere with a slightly viscid purulent secretion completely obstructing them. The posterior two-thirds of both lungs were purple and airless, as in atelectasis. The right lung weighed 450 gm., and the left lung weighed 350 gm. The tracheobronchial lymph nodes were enlarged and edematous. The myocardium, liver, and kidneys showed pronounced cloudy swelling. The brain weighed 1,200 gm. The leptomeninges were unchanged and the convolutions of the brain were normally rounded and the sulci of normal width and depth. There were no abnormalities of the cranial nerves or of the blood vessels at the base of the brain. The brain was unchanged on many surfaces made by cutting the

cerebrum, cerebellum, pons and medulla oblongata. The spinal cord was removed and no noteworthy macroscopic changes of the spinal cord or of the spinal nerves were found.

Microscopic sections through the cerebral cortex, basal ganglia, cerebral peduncles, pons, cerebellum and medulla oblongata showed a slight vacuolation of the myelin in the immediate neighborhood of the small blood vessels. There were also occasional small regions of demyelinization apparently not related to the blood vessels. The changes were most pronounced in the basal ganglia, pons and medulla oblongata and were not associated with cellular infiltrations. They resembled the much more pronounced lesions illustrated in a report by A. B. Baker[15] in 1943. The roots of the spinal nerves disclosed edema of the supporting interstitial stroma with slight swelling of some of the myelin sheaths and axis cylinders (figure 1). The large nerve cells in the gray matter of the cord as well as in the pons, medulla oblongata, and basal ganglia were unchanged. Some irregular swelling of the myelin sheaths of the longitudinal fiber tracts was found in the spinal cord. The histologic changes in the nervous system were considered to be compatible with a clinical diagnosis of the Guillain-Barré syndrome.

Microscopic examination of the lungs showed atelectasis with a polynuclear leukocytic exudate which completely filled the small bronchi and bronchioles, and this was the complication which was considered the probable cause of death. The myocardium, liver, kidneys, and the suprarenal glands revealed no noteworthy microscopic changes.

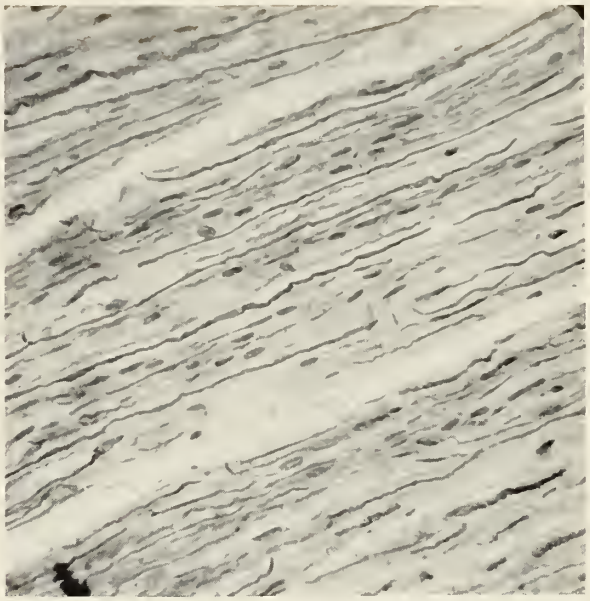

Fig. 1. Microphotograph of fibers of the cauda equina. Bodian stain shows swelling and tortuosity of the axis cylinders. Strands of nerve fibers are separated by edema. Infiltration by round cells is absent.

DISCUSSION

Considerable difficulty attends the determination of the value of any agent in the treatment of patients with the Guillain-Barré syndrome because of the well recognized variation in the clinical course of the disease and the tendency to spontaneous remissions. In those patients with respiratory paralysis, the mortality is high and any drug which may arrest or prevent this complication deserves investigation. At present no large series of patients treated with cortisone is available for statistical study. In the first of the 2 cases reported in this paper, cortisone seemed to halt the steady advance of the disease which had progressed to pronounced weakness of the muscles of respiration and a review of the hospital record shows that improvement began within twenty-four hours. In the second patient, cortisone was given within a few hours after the onset of muscular weakness in the legs was discovered.

In spite of the administration of cortisone, the condition of the patient was marked by increasing weakness of the legs and arms and finally difficulty in swallowing. After four days, evidence of paralysis of the intercostal muscles appeared. The amount of cortisone was increased and three days later she was able to eat soft foods and gained strength in her legs. Death followed a short time after tracheotomy was performed for laryngeal edema. Histologic examination of the central nervous system showed relatively few changes, the most important of which was edema of the spinal nerve roots. Since there were no cellular exudates and no evidence of marked changes in the spinal nerves, such as are reported in the recent studies of the pathologic changes in the Guillain-Barré syndrome, cortisone may have been responsible for this protection. The autopsy disclosed bronchial obstruction by a purulent exudate with pulmonary atelectasis as the immediate cause of death.

CONCLUSIONS

Reports of 2 patients with the Guillain-Barré syndrome complicated by pronounced respiratory weakness are presented. In both instances, the administration of cortisone was followed by improvement. Death of one of the patients was caused by a purulent bronchitis with pulmonary atelectasis. Histologic examination of the central nervous system disclosed edema of the spinal nerve roots and only slight changes in the myelin sheaths and axis cylinders. The mildness of these changes suggests that cortisone may have protected the nervous system against more extensive damage.

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(References continued on page 40A)

Importance of Bronchoesophagology to Other Branches of Medicine

Report of 32 Illustrative Cases

GRAHAM G. SMITH, M.D.

Minneapolis, Minnesota

Bronchoesophagology has assumed an enviable position of importance to practically every branch of medical practice. The dependence upon the endoscopist for accurate diagnosis and effective treatment by the internist, general practitioner, general and thoracic surgeons, pediatricians, and others cannot be denied. The purpose of this paper is to reveal by example and case reports the important responsibility the bronchoesophagologist assumes in accepting cases from or referring cases to his colleagues in other fields of medical practice.

The internist frequently calls upon the endoscopist to assist in completing his diagnosis of upper respiratory or bronchopulmonary disease. In this regard, it may be a question of determining an etiologic agent, a bacterial diagnosis, a source of bleeding, a cause of vocal cord paralysis, a reason for recurrent pneumonitis, unresolved pneumonia, or atelectasis. Or, the internist particularly interested in tuberculosis may want more accurate information regarding the extent of a tuberculous process or the reason for persisting positive sputum in the face of negative roentgen findings or the progressive effectiveness of chemotherapy in the treatment of endobronchial tuberculosis. Other problems of the internist may be referable to cardiospasm, esophageal hiatus hernia, regurgitation esophagitis, benign esophageal stricture, pulsion diverticulum, or bleeding from esophageal varices. And, of course, malignancy in the esophagus or the tracheobronchial tree concerns everyone.

The following reports illustrate the importance of endoscopy in paralysis of the vocal cords.[1,2]

CASE REPORTS

Case 1. R. B., a 31-year-old white male, was referred in February 1948 because of hoarseness and cough for a duration of ninth months. There was very little sputum and no hemoptysis. Sputum and gastric washings were negative for tuberculosis. A roentgenogram of the chest showed a large shadow in the apex of the right lung. Bronchoscopy revealed a paralysis of the right vocal cord, the cord lying in the paramesial position. The upper right lobe bronchus was obviously displaced inferiorly and posteriorly by the apical tumor. No endobronchial lesion was seen, but an extrabronchial mass caused pronounced compression of the bronchi. The bronchograms demonstrated a failure to completely fill the right upper segmental bronchi. The roentgen findings, right cord paralysis, and bronchoscopic findings suggested a Pancoast's tumor in the right apex. Exploratory thoracotomy proved this tumor to be a lymphosarcoma.

Case 2. O. E., a 49-year-old white male, was seen in consultation in March 1948 because of hoarseness for a duration of eighteen months, dyspnea and weight loss for one year, and hemoptysis for one week. A roentgenogram of the chest suggested widening of the mediastinum but clear lung fields. On bronchoscopy, a paralysis of the left vocal cord was noted. Pronounced distortion and widening of the carina were present with compression of both right and left main bronchi by the subcarinal mass. The tumor had eroded the right main bronchus and a biopsy was obtained from this area. The tumor proved to be an undifferentiated carcinoma. The patient was given radiation therapy and lived for five months after the diagnosis was made.

Case 3. E. B., a 56-year-old white male on the tuberculosis service, was referred because of hoarseness of one year's duration. Tuberculous laryngitis was suspected. However, laryngoscopic examination showed a paralysis of the right vocal cord. Roentgen examination showed a right apical lesion with pleuritic adhesions. Bronchoscopy was essentially negative except for positive acid-fast washings from the right upper lobe.

Case 4. S. E., a 34-year-old white female, was referred by an internist because of progressive voice changes and hoarseness. The patient was being treated for mitral stenosis. A laryngeal examination showed a left recurrent laryngeal nerve paralysis. Bronchoscopy proved evidence of pressure on the left recurrent nerve by cardiac enlargement.

With the advent of some of the newer chemotherapeutic drugs and antibiotics, the management of the tuberculous patient has improved with remarkable success. Many cases formerly thought to be hopeless have been cured by medicine and surgery and have been rehabilitated to a status of useful citizenry and economic security. It is gratifying to know that the bron-

GRAHAM G. SMITH, *a 1939 graduate of the University of Minnesota, is a specialist in bronchoesophagology and practices in Minneapolis.*

choscopist has played an important role in this progress. I have observed a number of patients with endobronchial tuberculosis who were being treated with streptomycin, para-aminosalicylic acid (PAS), or isonicotinic acid hydrazide (INH). I have watched these endobronchial lesions disappear to the point at which safe effective resection surgery could be undertaken for eradication of the diseased lung tissue. These patients are usually treated with a combination of two of these agents. The streptomycin is administered in doses of 1 gm. intramuscularly twice per week for a year to eighteen months. The para-aminosalicylic acid is administered in doses of 4 gr. orally three times daily for a like period. The isonicotinic acid hydrazide (Rimifon) is administered orally in doses of 100 mg. three times daily. The patient is not permitted to smoke. The oral drugs may be used in combination for the cooperative intelligent patient, thus eliminating the necessity of "shots."

The next two case histories are cited to exemplify the success of this treatment and the need for cooperation between the internist, the bronchoscopist, and the thoracic surgeon.

Case 5. C. A. is a 37-year-old white male with cavitation in upper left apex. Bronchoscopy showed red velvety lesions along the lateral wall of the left main bronchus. Biopsy of this area was reported by the pathologist to be tuberculous bronchitis. This patient was treated with streptomycin and para-aminosalicylic acid for fourteen months, during which time repeated bronchoscopic examination showed a gradual disappearance of the endobronchial lesions. This patient had an upper left lobectomy in June 1953 and has remained asymptomatic and sputum negative since.

Case 6. M. H., a 41-year-old white female, was referred to me by a friend in May 1951 because of sore throat and hoarseness. No history of contact was given. Indirect laryngoscopy revealed a beefy red lesion in the posterior commissure extending subglottically. Chest roentgenogram showed a large cavity in the upper right apex. Direct laryngoscopy and bronchoscopy with biopsies demonstrated tuberculous bronchitis. The patient was put on streptomycin and para-aminosalicylic acid. Later, because of the toxic effect of the streptomycin, she was switched to isonicotinic acid hydrazide. Bronchoscopy in December 1952 showed a complete disappearance of the laryngeal and bronchial lesions. The patient had a right upper lobectomy in January 1953. Since then she has returned to her home and is living a normal life with her husband and three children.

It is quite apparent that the last two cases were of equal interest to both the internist and the thoracic surgeon. There are a number of other chest problems in which the endoscopist finds himself a liaison between the internist or general practitioner and the chest surgeon. These problems will be discussed later.

Massive hemorrhage from the gastrointestinal tract is always very disconcerting to the referring physician. Esophageal varices can be very troublesome in this regard.[3] In the past, various attempts have been made to control bleeding through the esophagoscope by tamponade, cautery, or injection of sclerosing agents. I have found that the most effective means of control is by accurate insertion of the Sengstaken-Blakemore tube which has both a gastric and esophageal bag and can be controlled completely by attachment to a mercury or Tycos sphygmomanometer. At the same time contents of the stomach can be aspirated and tube feedings can be carried on. The following case history illustrates this life-saving device.

Case 7. G. S. was seen on emergency consultation in May 1954 because of profuse massive and continuous hematemesis. He was being transfused with the eleventh pint of blood when I first saw him. A Sengstaken tube was inserted and the bleeding was absolutely controlled. The tamponade was maintained for six days and then removed. The patient has subsequently had a splenorenal shunt operation and has returned to his regular employment in a boiler factory.

Endoscopists are often called upon to assist in diagnosis of and contribute to the treatment of patients with cardiospasm, esophageal hiatus hernia, diverticula, and benign esophageal stricture. By and large, surgery for hiatus hernia should be reserved for the large disabling types. Surgery such as cardioplasty for cardiospasm has fallen into disrepute because of the subsequent incompetence of the cardia and the accompanying regurgitant esophagitis. I have a number of patients with cardiospasm whom I have been treating with dilatations and dietary regime for years. These patients are relatively free of symptoms and are grateful for the help they have received.

Case 8. L. M., a 19-year-old white female, was referred in May 1954 because of uncontrollable vomiting and weight loss. This girl was completely incapacitated because of dysphagia, vomiting, and general weakness. Esophagoscopy was performed and her condition improved. Dilatations were carried up to 45 F. with Plummer dilators. A Hurst mercury filled dilator of 42 F. calibre was then secured for the patient, and she has since been dilating herself at frequent intervals and has continued to improve.

Case 9. E. S., a 61-year-old white male, was referred in March 1951 because of dysphagia, cough, vomiting, and weight loss. Chest roentgenogram showed pronounced increase in the bronchovascular markings of both bases. An esophagram revealed cardiospasm with tremendous dilatation of the proximal esophagus. Bronchoscopy revealed the presence of aspiration bronchitis. Dilatations up to 45 F. were obtained with Plummer bougies and then continued with a 42 F. Hurst mercury filled dilator. To date this man has managed very satisfactorily by frequently dilating himself with the Hurst dilator.

A number of patients have been seen with regurgitation esophagitis.[4] These cases have all

been associated with esophageal hiatus hernia and congenitally short esophagus or else postoperative results from surgery for hiatus hernia, resection of cardia for cardiospasm, or surgery for benign stricture of the esophagus.

Case 10. M. M., a 64-year-old white male, gave a three-year history of progressive dysphagia, epigastric pain, and substernal burning which increased when bending over or while in a recumbent position. He had one attack of hematemesis which prompted him to seek medical advice. Esophagoscopy on May 24, 1954, showed an incompetent cardia by virtue of the presence of gastric secretions in the esophagus. A regurgitant esophagitis and ulcerations were present at the esophagogastric junction which bled readily when touched with a suction tip. This condition was regarded as a hiatal hernia of the sliding type. This patient has improved markedly on dietary regime, antacids, and Probanthine.

Case 11. G. P., a 54-year-old white male, was first seen in April 1953. He complained of dysphagia, belching, and substernal burning when bending forward. An esophagram on April 10 showed hiatus hernia with probably associated developmental shortening of the esophagus. On May 23, an esophagoscopy revealed a reflux esophagitis, gastric secretions in the esophagus, and angry ulcerations at the gastroesophageal junction. This patient has improved on Probanthine, antacids, and an ulcer diet.

Case 12. I. S., a 37-year-old white female, was referred by a general practitioner because of hematemesis, dysphagia, and epigastric pain. An esophagram on March 23, 1954, showed a hiatus hernia with indications of a definite tendency toward regurgitation of the contents of the stomach into the esophagus. Esophagoscopy on March 24 showed regurgitation esophagitis, ulceration, and a definite inflammatory stricture of the distal 3 in. of the esophagus. This patient has improved after several esophageal dilatations, antacids, and general ulcer regime.

Case 13. K. C., an 87-year-old white female, was seen on September 9, 1954, ten days after transthoracic surgery. During this operation, the thoracic surgeon freed adhesions restricting normal contractions of the lower esophagus and releasing an impaction of food and barium which completely blocked any passage from the esophagus into the stomach. At esophagoscopy, a benign stricture was noted in the lower segment of the esophagus which would not permit further advancement of the esophagoscope. A hydrostatic dilator was then inserted, and under fluoroscopic vision the strictured area was carefully dilated by breaking up the adhesions with 18 to 20 lb. pressure. Dilatation has since been carried out with a 40 F. Hurst dilator, and the patient has been discharged on a normal diet.

Case 14. E. J., a 62-year-old white male, was operated on for hiatal hernia in June 1953. He subsequently developed symptoms of esophagitis with retrosternal burning, dysphagia, and hematemesis. I saw the patient first in March 1954 after a moderately severe hemorrhage. Esophagoscopy revealed that the hemorrhage was coming from angry ulcerations at the esophagogastric junction. This patient has improved on an ulcer diet and repeated esophageal dilatations. He has not hemorrhaged to date.

Case 15. E. G., a 59-year-old white male, underwent a cardioplasty or esophagoplasty for achalasia in 1947. I first saw this patient in May 1950, at which time he complained of retrosternal burning, dysphagia, anorexia, and weight loss. He also was suffering from aspiration pneumonia. Bronchoscopy revealed a purulent diffuse bronchitis. At esophagoscopy, marginal ulceration and stricture at the operated site were found. This patient has been treated with ulcer diet, antacids, Banthine, and repeated dilatations for the past four years with resultant improvement in general health, weight gain, and freedom from his presenting symptoms.

Case 16. M. D., a 51-year-old white male, had a partial gastroesophagectomy for carcinoma of the cardia in 1948. I first saw this patient in September 1948 because of esophageal obstruction. At the time of esophagoscopy, the lower segment of the remaining esophagus was filled with reflux gastric secretions and solid food fragments. There was an inflammatory stricture at the site of the gastroesophageal anastomosis and a marginal ulcer. Several attempts at dilatation gave very temporary relief. A second procedure was attempted to eliminate the secreting glandular elements of the stomach. However, he survived only two days after his secondary procedure.

Case 17. E. C., a 49-year-old white male, is included in this series because of some similarity to the preceding case. This patient had a total gastrectomy for carcinoma in December 1946. At the time of surgery, the esophagus was anastomosed to the jejunum. The patient was quite well until March 1947, when he developed obstructive symptoms. At esophagoscopy, a diffuse inflammatory reaction was noted just above the esophagojejunal junction, and a reflux of bile was present in this area which appeared to be propelled upward into the esophagus by reverse peristaltic waves of the jejunum. The anastomosis was stretched with sounds under direct vision, after which the patient did very well. He was last heard from in December 1950, four years after surgery, at which time he was living a fairly normal life.

Pulsion diverticulum of the esophagus is a relatively rare disease. Most of the pulsion diverticuli that I have observed are really pharyngeal diverticuli and represent a herniation of the sac through the thinned out cricopharyngeal musculature. The majority seem to be found on the left side. I have found two cases that projected posteriorly in the midline and considerably lower down than the average pulsion diverticulum.

Case 18. C. W., a 73-year-old white male, was seen in July 1954 because of dysphagia; retention of food, especially solids and aspirin tablets; and frequent regurgitation of undigested food. Esophagram showed a large sized pulsion diverticulum which projected posteriorly at the level of the lower border of the first thoracic vertebra. The esophagus was slightly narrowed at the site of origin of the diverticulum. Esophagoscopy bore out the findings of the esophagram, and barium and food particles were washed out of the sac preparatory for surgery.

Case 19. D. J., a 72-year-old white female, I saw first in June 1954 because of esophageal obstruction. She gave a history of having had a foreign body in the esophagus in May 1953. At that time, the esophagoscopist perforated the esophagus, and subsequently she had to have a mediastinotomy with "tubes in her chest." Esophagoscopy in June 1954 showed a posterior esophageal diverticulum with a cicatricial web at the site of the previous perforation at about the level of the second dorsal vertebra. The obstruction was relieved by removal of the impacted food and the rupture of the web with the esophagoscope. The patient was carried on dilatations until September 1954, at which time the diverticulum was excised. She recovered completely from surgery and is at present asymptomatic.

Some thoracic surgeons prefer to do their own bronchoscopy. In our locality, chest surgeons prefer to have bronchoesophagologists perform this work. These surgeons have grown to depend upon the bronchoscopists' interpretation of findings and thorough diagnosis. By thorough, I mean the careful inspection of the tracheobronchial tree from the larynx to the segmental bronchial orifices, using the Broyle's telescopes wherever necessary. This inspection also includes the careful collection of secretions and bronchial washings from a specific area for cytologic study, acid-fast examination and culture, culture of a predominant organism, and sensitivity tests. Careful accurate biopsies are taken, accurate word-picture descriptions are noted, and operability from the bronchoscopic standpoint is determined. Another important part of the diagnosis is the accurate mapping of the bronchopulmonary segments with radio-opaque material under fluoroscopic vision. This procedure requires the cooperation of the radiologist. In conjunction with bronchograms, we have recently turned to Dionasil Aqueous which is superior to the Lipiodol in that it assimilates quicker, absorbs faster, and permits the thoracic surgeon to operate almost immediately after bronchoscopy. Bronchospirometry is another useful procedure, particularly when resection surgery has been performed and further resection surgery is contemplated.

Some pathologic situations arise in which the endoscopist is not only the diagnostician but also the therapist. Certain inoperable lesions may arise for which the endoscopist must undertake certain palliative measures. Some cases are completely amenable to bronchoscopic or esophagoscopic treatment. These cases include certain adenomas of the bronchi or other benign tumors, foreign bodies, broncholithiasis, postoperative stenoses, bleeding, and postoperative atelectasis.[5,6] Included in this group of patients are those cases of inoperable carcinoma of the esophagus which we have successfully palliated by means of an endoscopic application of the Mackler esophageal tube.

Early diagnosis of lung cancer is most desirable. An unusually large group of both early and late cases have been encountered. These are illustrated by the following case histories:

Case 20. G. D., a 50-year-old white male, was first seen in April 1946. He complained of cough, chest pain, and dyspnea after a cold in March 1946. Chest roentgenogram was reported negative. Because of persistent complaints, I performed a thorough bronchoscopy April 25, 1946, and no pathology was noted. Bronchograms at this time were also negative. However, the man's symptoms continued and in June 1946 he coughed up some blood. Another chest roentgenogram was negative. A second bronchoscopy on June 18, 1946, revealed a small discrete tumor within the right upper lobe bronchus which could be seen only on forced expiration. A biopsy was obtained which proved to be bronchogenic carcinoma. A pneumonectomy was performed on June 20, 1946, and I am happy to say that this man enjoys good health and hunts ducks with me eight years after his surgery.

Case 21. L. S., a 61-year-old white male, first noted a lump in front of his left ear in April 1946. A biopsy of this mass by a general surgeon proved the tissue to be metastatic undifferentiated carcinoma of the parotid gland. The patient had no chest symptoms but a routine roentgenogram of the chest revealed a left hilar shadow. Bronchoscopy and biopsy proved this to be a primary small round cell carcinoma of the left main bronchus. Treatment consisted of radiation. Bronchoscopy on June 11, 1946, showed the tumor to be considerably smaller. The patient died in December 1946 with cerebral metastases.

Case 22. I. I., a 74-year-old white female, was seen first in August 1951 because of severe blinding headaches which became much worse at night. She had been treated elsewhere for "sinus headaches." A careful history disclosed the fact that for over a year she occasionally coughed up some bloody sputum. This was presumed to have come from the sinuses. A careful examination of the ear, nose, throat, and sinuses failed to reveal any pathology or source of bleeding. A chest roentgenogram taken at a public health center August 25, 1951, was reported as negative. About the first week in September, I saw this patient cough up some blood. She was having excruciating head pains at this time. She was admitted to the hospital on September 12, 1951, and another chest roentgenogram showed absolutely negative findings. Bronchoscopy was done and biopsy of a tumor mass discovered in the right lower lobe bronchus was reported by the pathologist to be adenocarcinoma. Palliative radiation to the head seemed for a while to relieve the headaches. The patient had a steady downhill course and died almost two years later.

Case 23. B. W., a 49-year-old white male, was referred by his internist because of recurrent pneumonia in the right lower lobe. This man was a heavy smoker and coughed up great quantities of sputum after his first morning cigarette. He denied hemoptysis. A bronchoscopy on August 25, 1949, showed an inflammatory stenotic area in the right lower lobe bronchus. Bronchial washings were obtained from beyond the stenotic bronchus that would not permit advancement of bronchoscope or telescope. Biopsy showed only an inflammatory reaction in the bronchial mucous membrane. However, cytologic study of the bronchial secretions showed definite tumor cells. Bronchograms demonstrated a typical rat-tail deformity of the lower lobe bronchus. The patient underwent pneumonectomy and has remained well since.

Case 24. J. H., a 71-year-old white male, was referred by a general practitioner because of his inability to swallow either fluids or solids, a symptom which arose while this patient was being treated in the hospital after transurethral resection of his prostate gland for benign hypertrophy. This man gave an interesting history of having had a bowel resection five years previously for carcinoma with apparent complete recovery. A routine admission film revealed at this time a lesion in the upper left lobe which was thought to be possible bronchogenic carcinoma. When seen in the hospital, the patient stated that he had had some difficulty in swallowing and had had some hoarseness for the past three months prior to his

admission. Laryngeal examination revealed a fixation of the right arytenoid, and, at esophagoscopy, a large fungating lesion was found in the upper esophagus just below the cricopharyngeal pinchcock. A biopsy of the tumor revealed this lesion to be a primary carcinoma of the esophagus with metastasis to the left lung. A feeding tube was inserted through the lesion into the stomach and the patient was fed via the tube. However, he was extremely uncomfortable and complained bitterly of the tube. A thoracotomy which would permit insertion of a Mackler tube was thought too hazardous, and a gastrostomy was thought unsatisfactory. Therefore, it was decided to attempt to insert a Mackler tube through the lesion. This was done by means of a short Jesburg esophagoscope and a long 5 mm. bronchoscope inserted into the funnel end of the Mackler tube and passed through the esophagoscope. After withdrawing the bronchoscope, this was then grasped with an alligator forceps and forced through the carcinomatous lesion. The patient was able to swallow very well forty-eight hours after placement of the tube, and he has enjoyed a reasonable diet for ten weeks since insertion of the tube. He has had no difficulty in retaining the tube in the position in which it was placed, and he has neither regurgitated the tube nor lost it in the stomach as has happened sometimes in attempts to suture this tube into the esophagus through a thoracotomy.

Case 25. A. M., a 54-year-old white female, was also referred by a general practitioner because of dysphagia, inability to swallow either liquids or solids, and emaciation. A preliminary esophagram revealed that only a bare trickle of Lipiodol passed through what apparently was a tremendous intrinsic lesion of the midesophagus. Thoracic surgeons refused to operate as they believed the lesion was not resectable. Esophagoscopy and biopsy revealed a scirrhous carcinoma of the esophagus. The same technic as used in case 24 was applied to this patient with equally good results. The patient is still eating well and has gained several pounds five weeks after insertion of the tube.

During the past eight years, I have bronchoscoped 178 patients with carcinoma of the lung. Of these patients, 92 were referred by thoracic surgeons, 66 were referred by internists, 17 were referred by general practitioners, and 3 came to me directly. Of these patients, 116 have been institutional cases, that is, they have been patients in teaching institutions, veterans' hospitals, charity hospitals, or state hospitals; 62 have been seen in private practice. Of the 178 patients, 72 were found to be inoperable at the time of bronchoscopy. An exploratory thoracotomy was performed in 106 patients. Surgery was completed in only 35 of these patients; the other 71 were found inoperable at the time of the exploration. Of the 35 patients in whom resection was completed, 12 have lived three years, 8 have lived five years, and 15 have not been heard from.

The bronchospirometric tube of Zavod has been a useful instrument in gauging relative vital capacities of remaining bronchopulmonary segments after partial resection for bronchiectasis.

Case 26. E. L., a 23-year-old white male, was an outstanding example of the application of this procedure. This patient had had a left lower lobectomy and lingulectomy and yet persisted in having annoying symptoms in the right lower lobe from bronchiectasis. Zavod's method of bronchospirometry was applied, and it was determined from this procedure that secondary segmental resection to eradicate the bronchiectatic focus in the right lower lobe could be done safely. He had his final operation in March 1948 and has remained well since.

Something should be mentioned here about "middle lobe syndrome"[7] before we leave the realm of the thoracic surgeon. In glancing over our bronchoscopic records of the past five years, we appear to be frequently encountering nontuberculous right middle lobe atelectasis. The apparent reason for this middle lobe syndrome is the fact that the middle lobe bronchus lies at the apex of the lymphatic pathways from both the upper and lower lobes and that the strategically located lymph nodes enlarge and impinge upon this bronchus causing bronchial compression, stenosis, poor aeration and drainage, and eventually infection, atelectasis, and bronchiectasis of the right middle lobe.

Case 27. R. Z., a 45-year-old white female, I treated for nasal polyposis, suppurative pansinusitis, and middle ear infection in April 1954. In addition, she had a severe bronchitis and cervical lymphadenopathy of a severe degree. She improved after draining the ear, removing the nasal polyps, irrigating the sinuses, and maintaining her on large doses of antibiotics. In June 1954 she returned, this time complaining of pain over the right side of the chest and coughing up voluminous quantities of thick purulent sputum. A chest roentgenogram was negative. Bronchoscopy revealed a definite compression of the right middle lobe bronchus. Bronchograms demonstrated an atypical appearance of the intermediate bronchus and its failure to fill with oil. At thoracotomy on June 22, 1954, a completely atelectatic middle lobe was found with the middle lobe bronchus compressed by lymph nodes below and the pulmonary artery above.

Case 28. M. O., a 42-year-old white male, was referred by an internist because of recurrent pneumonia and atelectasis of the right middle lobe. The roentgenogram of the chest showed atelectatic changes in the right middle lobe with unresolved pneumonia probably due to a tumor. At bronchoscopy, pronounced compression of the intermediate bronchus was noted. A biopsy and bronchial washings were negative for tumor. At thoracotomy, a completely atelectatic right middle lobe was found with the intermediate bronchus compressed both cephalad and caudad by enlarged lymph glands.

Fracture of the bronchus is a relatively rare occurrence and pathologic fracture of the bronchus[8] is almost unheard of. I have seen two patients with ruptured bronchi. The first case was previously reported by Priest[9] in December 1950. The second case which I call pathologic fracture of a bronchus will be described.

Case 29. C. J., a 47-year-old white male, had been perfectly well until March 1948 when he sustained a crushing injury to his chest. While lifting the radiator out of an automobile in the garage in which he worked, he lost his balance and fell backward with the radiator falling on his chest. He felt shaken and sore across the chest for a few days but continued to work. However, he

began to cough and spit up blood, and on March 19, 1948, two weeks after the accident, he was admitted to the hospital because of hemoptysis and severe dyspnea. A roentgenogram of the chest at this time showed an atelectasis of the lower half of the right upper lobe and the right middle lobe. Evidence of tension pneumothorax was present but no hemothorax. Bronchoscopy revealed a rupture of the right main bronchus 1.5 cm. down from the carina. A jagged loose fragment of the fractured cartilage was seen projecting into the lumen of the bronchus. This was surrounded by what I first interpreted to be granuloma but which I biopsied on the suspicion that it could be bronchogenic carcinoma. This suspicion proved to be correct, and subsequently this patient had a pneumonectomy and recovered. Probably the diagnosis of bronchogenic carcinoma might have been delayed for months had the accident not induced the pathologic fracture.

Bronchi have been successfully reanastomosed by suturing after being inadvertently sectioned by the thoracic surgeon. I have observed two such cases postoperatively in which patency was preserved with little or no stenosis or loss of function. A granuloma developed in one patient along the suture line and required repeated cautery through the bronchoscope before finally healing with very slight stenosis.

Case 30. C. R., a 33-year-old white male, had a left lower lobectomy performed for bronchiectasis. During the resection, the surgeon inadvertently severed the left main bronchus 3 cm. below the carina. The main bronchus was then reunited. A small granuloma developed along the posterior median wall. This was reduced by cautery through the bronchoscope every two weeks for three months, at the end of which time complete healing was evident with minimum stenosis and a perfect functioning upper left lobe and lingula.

Up to the immediately preceding case report, I have emphasized the importance of bronchoesophagology from the standpoint of diagnosis. Endoscopists have an equally important responsibility from the standpoint of therapeutics, such as the bronchoscopic treatment of the granuloma in case 30. The general practitioner and the pediatrician frequently call upon the endoscopist to remove a foreign body from air or food passages. The surgeon may call upon the bronchoscopist to relieve a postoperative atelectasis. Or, the pediatrician or obstetrician may call upon the bronchoscopist to diagnose and relieve atelectasis in the newborn. The neurologist may require the endoscopist's services to relieve lung complications in some bulbar syndromes, such as occur with bulbar poliomyelitis, brain tumors, or cerebral accidents. The bronchoscopist might quite possibly be the chief therapist in removing, for example, a small bronchial adenoma.

Case 31. W. M., a 37-year-old white male, was referred by an internist in August 1951 because of cough and hemoptysis. Sputum and gastric lavages were negative for tuberculosis. Roentgenogram of the chest was negative. The patient was bronchoscoped while active bleeding was in progress in order to ascertain the source. A small bronchial adenoma about the size of a pea and pedunculated was seen coming off the medial wall of the left lower lobe bronchus. This was seized by the bronchoscopic cup-biting forceps and avulsed. Bleeding was controlled by Adrenalin tamponade and cautery. The specimen proved to be a benign adenoma. Subsequent examinations have shown no evidence of recurrence.

A capillary hemangioma of the left lung was one of the most interesting cases I have encountered.

Case 32. A 44-year-old white male had been on a tuberculosis service for twenty years, during which time he was presumed to have tuberculosis and was drawing compensation for total disability for active tuberculosis. He had had some nearly fatal hemorrhages in that time, but no place in the records could I ever find a positive acid-fast report. The chest roentgenogram showed a nearly completely atelectatic left lung. As far as I know, I was the first to use a bronchoscope on this patient. At bronchoscopy on May 27, 1946, a vascular tumor mass was encountered which completely blocked the left main bronchus. A biopsy was taken with resulting brisk bleeding. This was controlled with Adrenalin tamponade and then electrocoagulation through the bronchoscope. The biopsy report was capillary angioma. The thoracic surgeons endeavored to remove the left lung but after freeing the lower lobe, the tumor was found to be so adherent to the chest wall and such severe bleeding was encountered that they felt the operation should be stopped. I next bronchoscoped this patient on June 25, 1946. At this time, I destroyed much more tumor and was able to aerate the upper lobe. This man has had repeated bronchoscopic coagulation of this tumor for eight years and has enjoyed excellent health with no bleeding since June 1946.

SUMMARY

An attempt has been made to emphasize the important position that bronchoesophagology has attained in relation to other medical specialties and to medicine in general. Case histories of 32 patients have been reviewed, exemplifying the contributions that endoscopists have made toward the advancement of medical practice.

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Trends in the Treatment of Acne Vulgaris

NATHAN PENSKY, M.D., and
NATALIE GOLDBERG, M.D.
Brooklyn, New York

Acne vulgaris is probably the most frequent cutaneous disease seen by physicians. Yet opinion differs greatly concerning the etiology and specific treatment for this cosmetically annoying and psychologically crippling disease. The clinician is often confused by the voluminous discussions and conflicting reports in the medical literature.

ETIOLOGY

According to Sulzberger and Baer,[1] clinical and experimental research indicates that the primary mechanism in the development of acne vulgaris is probably endocrine in nature – principally an imbalance between androgenic and estrogenic substances with the emphasis on an androgenic preponderance. White and associates,[2] however, feel that "The literature fails to reveal a definitive experimental basis for this theory. A review of the work of several investigators demonstrates the need for further work and more knowledge along these lines." They performed urinary 17-ketosteroid assays on 26 young men with acne vulgaris and found no evidence to substantiate the concept that the condition is related to an excess of androgenic hormone.

Sutton, Jr.[3] feels that acne vulgaris is a systemic disorder of endocrine and metabolic function "wherein the sebaceous glands are the seat of the clinically conspicuous dysfunction." Brunsting[4] states, "We speak of this (endocrine mechanism) rather glibly, yet do not understand the exact mechanism and all the implications. There may be wide variation in the ranges even in the apparently normal person without acne. Therapeutically our attempts in restoring this equilibrium have been equivocal." It is recognized that many other mechanisms, many of which are yet unknown, convert this endocrine dysfunction into a full-blown entity.

ANTIBIOTIC THERAPY

The role of pyogenic organisms in the acne complex leads to much speculation and disagreement. Peck[4] feels that bacteria play an important part in its development by acting either as sensitizing antigens or as direct infecting agents. He bases his contention on the many instances in which acne lesions have involuted after the parenteral administration of antibiotics and/or the oral and local use of broad spectrum bactericidal agents. Sutton, Jr.,[4] however, feels that bacteria, when present, are purely coincidental.

In treating severe cystic and pustular acne we use oxytetracycline (Terramycin). Our choice of antibiotic is based on the work of Welch,[5] Goldberg,[6] and Ritchie and Wallace.[7] Welch[5] studied the distribution of oxytetracycline in the tissues of the rabbit and found a much higher concentration of the antibiotic in the skin than in the blood. Goldberg[6] presented evidence that the oral administration of oxytetracycline caused involution of cystic and pyodermic lesions in acne vulgaris. Ritchie and Wallace[7] treated 50 children with burns and scalds with oxytetracycline and found no evidence of established infection using this type of prophylactic therapy.

Our immediate results in treating severe cystic and pustular acne routinely with oxytetracycline were encouraging, and so we enlarged our series to include 55 patients. They varied in age from 12 to 45 years; 30 of the patients were female. We tried to establish the smallest dose of the drug which would cause involution of the cystic and pustular elements.[8] We soon discovered that to control some individuals required 1 to 2 gm. a day, while others responded to as little as 0.5 gm. Some of our patients were maintained on oxytetracycline for as long as fourteen months.

However, our long-range results were disappointing. The pustular and infected cystic ele-

NATHAN PENSKY, *a 1933 graduate of George Washington University School of Medicine, is a specialist in dermatology in Brooklyn, New York.* NATALIE GOLDBERG, *a 1930 graduate of New York Medical College, Flower and Fifth Avenue Hospitals, also specializes in dermatology in Brooklyn.*

ments promptly reappeared and often became worse as soon as the medication was discontinued. In addition, unpleasant side reactions developed in 13 of our patients. The symptoms consisted of vaginal and rectal pruritus, diarrhea, nausea, and abdominal cramps. Therefore, we question the use of this broad-spectrum antibiotic over long periods of time. Although the severity of the reactions depended largely on the total daily dose, we noted reactions in patients who received as little as 200 mg. a day.

As a result of our experiences, we have discontinued the routine use of broad-spectrum oral antibiotics and reserve their employment solely for the severe pyodermic phase. We administer them only in the hope that we may obtain a remission of the symptoms while we utilize other modes of treatment.

LIVER THERAPY

According to Peck and associates,[4] the average case of acne runs a course of three to five years. However, in reviewing the histories of our acne patients, especially the older ones, we have found that many have had acne for a much longer period and that the condition is still severe.

In an attempt to shorten the duration of this condition and thus lessen its sequelae, we investigated other methods of treatment. We became intrigued by the use of liver preparations in the control of acne. Over the years, a considerable number of observers have tried this material. The results varied but in general they were encouraging. Sutton[9] felt that crude liver extract was beneficial. Hume[10] felt it was effective as an adjunctive measure in the therapy of acne. Walters[11] found that crude liver extract heated or unheated was beneficial. Lewis[12] stated that crude liver extract is sometimes beneficial even when no anemia is present. Marshall and Schadeberg[13] and Lichtenstein and Stillians[14] obtained good results with a fractionated derivative from crude liver.

Nierman[15] obtained definite improvement using Kutapressin in the treatment of 22 patients with cystic acne. Kutapressin is prepared from crude liver extract by a series of fractionations which concentrate the active principle ("S" factor) and render it better tolerated than even the purified extracts. In the process of fractionation, both the hypertensive and hypotensive principles of liver are removed. Kutapressin causes vasoconstriction of peripheral vessels and enhances the action of epinephrine on the smooth muscle cells in the terminal blood vessels, particularly those in the skin.[16]

In 1953, we reported our results using Kutapressin in the treatment of refractory acne.[17] Kutapressin was used to treat 52 private patients who had failed to respond to all other forms of treatment. We obtained moderate to good improvement in 63 per cent of our patients. Burks, Jr., and Knox[18] treated 226 patients with this "S" factor of liver supplied as Kutapressin. They employed a minimum of supportive treatment and reported 54.7 per cent moderate to pronounced inhibition of the disease.

Since our previous report,[17] we have extended the use of Kutapressin in the treatment of all forms of acne vulgaris to 72 additional patients, 41 of whom are female. They have been followed for a minimum of ten weeks; many have been observed for over eighteen months. In spite of the fact that 22 had received all forms of treatment including x-ray therapy elsewhere, their acne continued to blossom. All received biweekly injections of Kutapressin subcutaneously. The dose was 2 to 3 cc. In addition, all patients were treated with local modalities such as cryotherapy. Our impression, which was confirmed by the comments of the patients, was that clinical improvement became apparent in about six weeks and thereafter continued slowly but noticeably.

Statistically, improvement was impossible to evaluate as each case was a distinct entity and no 2 cases looked the same clinically. However, there was no doubt that the improvement was in some measure due to the liver therapy and not to spontaneous clearing. We agree with Burks, Jr., and Knox[18] that studies should be made to isolate the "S" fraction. Used in pure form in massive doses, more spectacular results might be obtainable.

Perhaps one of the actions of the "S" factor in liver is dependent upon its peripheral vasoconstricting effect. It may tend to prevent the outpouring of sweat which, according to Sulzberger,[1] could cause maceration and swelling of the keratin layer of the skin and thus cause plugging of the follicular openings.

FOOD FACTORS

The apparently normal individual can usually ingest most types of food without an acneform eruption. However, with some degree of regularity the symptoms of those with acne are aggravated by the ingestion of chocolate, cheese, shellfish, and nuts. Testing to prove susceptibility is of no value. The exact mechanism of this aggravation is not understood. As a matter of routine we eliminate chocolate, nuts, and sea food from the diet of these patients.

DRUG FACTORS

Iodides and bromides often cause existing acne to flare. They may also cause an acneform eruption in normal individuals. Opinions differ in this regard. Some capable investigators have even reported beneficial results due to the intake of iodine. Perhaps the differences can be reconciled if we consider the section in which the patient resides. Iodine may be helpful in the Great Lakes region where intake of iodine is inadequate and where hypothyroidism exists. In normal iodine intake areas, an excess may cause a flare-up. Sutton and Sutton[19] state that sensitivity of acne patients to iodides is due to hypothyroidism and that when iodides and thyroid extract are given to a hypothyroid patient, an eruption does not occur.

EMOTIONAL FACTORS

While little is known about the effect of the autonomic system on sebaceous glands, it is recognized that emotional factors may precipitate exacerbations of acne vulgaris. The physiologic functions of the skin are under the influence of the autonomic nervous system, and quite possibly emotional factors influence acne vulgaris through this medium. Sulzberger[1] states that "Among the known mechanisms by which emotional factors could conceivably affect acne vulgaris are the demonstrated influences of nervous mechanisms on growth of secreting sebaceous elements, the easily demonstrable production of congestion through vasodilatation in the 'flush area' of the face and the undeniably strong and rapid effects on sweating. The swelling of the horny layer which repeated outpouring of sweat produces could possibly lead to constriction and plugging of the follicle openings and thus also lead to the formation of new acne lesions in a manner somewhat similar to that which is postulated in the production of lesions in 'tropical acne.'"

Emotional factors may be sufficient to "push over" potential acne lesions into actual lesions. While the emotional state of the patient may affect acne, the embarrassment of facial disfigurement and its consequent disappointments may have a profound effect upon the psyche and the emotional state of the emotionally unstable adolescent.

Sweating is an important factor in acne and free sweating should be discouraged, for increased sweating also increases sebum secretion. It is common knowledge that young men who exercise vigorously are more disposed to acne eruptions than those individuals who live a sedentary life.

VITAMINS

Vitamin A regulates the cornification of the skin. Good results have been described utilizing large doses of this substance. We have found this remedy very disappointing.

X-RAY THERAPY

In the discussion of Peck's paper on the treatment of acne with estrone, Eichenlaub[4] stated, "Personally I think that properly used, x-ray is going to be much less harmful to the patient in the end than the prolonged use of antibiotics or the prolonged use of estrogens." Peck[4] responded that he was perfectly happy with its use and he felt it was quite safe in the hands of those who know how to use x-ray.

We feel that x-ray therapy, if used by experts, is perhaps the best modality. It shortens the acne duration better than any other single therapeutic procedure. We limit the use of x-ray to patients over 18 years of age who have not responded well to a combination of other treatments. We have never experienced trouble with its use.

LOCAL TREATMENT

Routinely the patient is instructed to use plenty of soap and water. A flesh colored shake lotion with 2 to 5 per cent Resorcin and sulfur or a 3 per cent Resorcin-salicylic acid-alcoholic solution is used. This controls the associated seborrhea and the mild desquamation is also beneficial.

The use of powdered carbon dioxide in acetone to form a slush (cryotherapy) is especially indicated in cystic acne. When used carefully, it helps resolution of some of the cystic components and at the same time causes some peeling of the skin which is helpful.

ENDOCRINE

The use of hormones in the treatment of acne vulgaris is both praised and damned. Locally either sodium estrone sulfonate or diethylstilbestrol has been used as a cream by Peck and associates,[4] Shapiro,[20] Sawicky and associates,[21] and Philip.[22]

Becker[4] saw no difference between a placebo lotion and a lotion containing hormone. Sulzberger and Witten[23] believe that the use of hormones parenterally, orally, or topically has proved of only partial value in the management of acne. Eichenlaub[4] found their use locally and internally very disappointing.

We have not been very successful with either diethylstilbestrol or Premarin. However, an occasional case of premenstrual or chin acne ac-

companied by irregular periods has shown temporary improvement when Premarin in doses of 0.625 mg. has been given after ovulation and continued until menstruation has occurred.

THYROID EXTRACT

Sutton and Sutton[19] state, "Thyroid extract is indicated in all cases; it is given to tolerance without regard to B.M.R. or blood chemistry." They feel that thyroid extract is especially needed if the patient is depressed, fatigues readily, is anemic, and feels cold. They usually give 2 gr. of desiccated whole gland substance with the evening meal. Occasionally patients are given additional doses after breakfast and lunch. They prefer desiccated whole gland to thyroid extract. They state further, "The dose must be estimated by clinical trial, giving just less than the amount which produces symptoms of excess. The dose must be adequate." The dose may be decreased to one-half after two weeks.

Terramycin tablets and capsules were supplied in part by Chas. Pfizer & Co., Inc. and purchased in part by patients on prescription.
Kutapressin was supplied by Kremers-Urban Co.

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Plantar warts can be effectively treated by curettage. Everett R. Seale, M.D., and J. B. Richardson, M.D., of Houston report that the procedure is simple, relatively painless, and can be done in the office. The area is cleansed with 70 per cent alcohol and sprayed with ethyl chloride. Then, 2 cc. of a 1 per cent solution of procaine without epinephrine is slowly injected under the lesion through a ½-in., 26-gauge needle. The keratinized surface is removed, and the verrucous tissue is shelled out with a small curet. Overhanging edges are trimmed with a curved scissors, the wound is filled with 5 per cent Mercurochrome, and a pressure dressing is secured by adhesive tape which completely encircles the foot. An antibiotic ointment and a simple dressing are applied twice daily until healing of the site is complete.

Everett R. Seale, and J. B. Richardson: South. M. J. 48:575-577, 1955.

Use of Protective Principles in Milk and Colostrum in Prevention of Disease in Man and Animals

WILLIAM E. PETERSEN, Ph.D., and
BERRY CAMPBELL, Ph.D.
Minneapolis, Minnesota

Protection against disease through the acquisition of protective immune bodies via the digestive tract is extensively practiced in nature. The young of several species, including the domesticated ruminants, are born without any antibody in their blood. Not until after the colostrum or first milk has been ingested does the gamma globulin fraction appear in the serum. That this acquired antibody is protective and will pass through the wall of the digestive tract was shown by Ehrlich.[1] Widespread opinion has been that only in the newborn calf is such absorption possible. We wish to report the results of a series of experiments which indicate that man may be protected from disease by the use of milk from specifically vaccinated cows.

The immense amounts of antibody produced in this way are shown by the fact that the concentration of the immune bodies in the colostrum is found to be as high as 120 times that of the blood. In cows producing many gallons of the material, amounts of the immune principles are to be found far in excess of any other natural source. It has been observed that all of the specific antibodies detectable in the blood serum are present in the colostrum, a fact which has led to the supposition that the origin of the antibodies was in the blood. However, as early as 1916, Giltner and associates[2] showed that the introduction of Brucella abortus antigen into one-quarter of a cow's udder resulted in a return of agglutinins from the injected udder first, with a slower return in the other three-quarters. The local production of colostrum antibody was made certain as we[3] demonstrated a plasmacytosis of the colostrum producing udder, both at parturition and after temporary cessation of milking. In the cows which we studied by biopsy, the total mass of the plasmacytes was estimated at more than a kilogram, thus accounting for the extraordinarily large amounts of antibody.

A proper description of the situation in regard to the cow's udder is that this organ is an exocrine reticuloendothelial gland. The many advantages of such a preparation are apparent to all who have had to study the production of immune substances in the diffuse tissues of the body with only the blood levels to indicate the amount and time of the secretion. Over and above the conveniences which this gland offers for immunologic reactions, however, are the practical uses to which it may be put. At the time of our earlier studies, the question of the possible use of these phenomena in the prevention and the treatment of disease was considered. At the present time we are convinced that use of these phenomena in both the human and veterinary fields is possible. The means for this utilization will be discussed after consideration of the new phenomena which we have observed.

In these laboratories, Porter[4] explored the spectrum of antigens responsible for the immune properties of colostrum and milk and found that the production of the antibodies could be specified by the deliberate exposure of the cow to various antigens. Thus, such foreign bacterial species to the cows as the typhoid-paratyphoid organisms, pneumococci, or even simple protein antigens such as egg white and horse serum produced an appearance of specific immune bodies in the milk and subsequently in the serum. He found, as did Giltner and associates[2] in 1916, that the return of antibody was extraordinarily rapid after infusion of the antigen into the udder, significant amounts being present in the milk in twenty-four hours. This finding we have since confirmed for other antigen species. We have explored the exposure of the cow's udder to antigens during the dry phase and have found that very high titers can be achieved in this way in

WILLIAM E. PETERSEN *is professor of dairy husbandry at the Institute of Agriculture, University of Minnesota.* BERRY CAMPBELL *is associate professor of anatomy at the University of Minnesota.*

the colostrum and milk upon the cow's freshening. As an example, in one dry, pregnant cow we have made 5 perfusions of a suspension of heat-killed Salmonella pullorum 5 times in each quarter at seven-day intervals. Upon parturition, the colostrum was found to agglutinate the antigen in dilutions of over 1 to 100,000. As lactation proceeded, the concentration of the antibody dropped down to 1 to 1,000 and subsequently lower in the succeeding months, but as the cow was a heavy milk producer (40 lb. per day) the amount of immune substance was considerable. We have found that repeated administration of the antigen gives a better return than if only single doses are given. This is equally true when the antigens are administered to the lactating udder. We have encountered local reactions when the intervals were spaced at more than a week apart, but no deleterious effects of these anaphylactic reactions on subsequent milk production have been observed.

As mentioned previously, the range of bacterial species to which the cow's udder reacts with this outpouring of antibody is wide. We have also found that combinations of antigens may be administered simultaneously. Each specific type of immune body is returned in the milk. As many as 8 species of killed bacteria have been infused into the udder with no indication of interference of one with another. Our impression of a potentiating phenomenon in such circumstances must await the test of more quantitative study. The effective stimulation of antibody secretion by such polyvalent vaccines is, however, a favorable circumstance. Of course, the natural antigenic stimulus to the cow is also demonstrably polyvalent.

Virus antigens have been used with indication of antibody return. Mitchell and associates[5] have shown that the cow's udder is a favorable medium for growth of certain species of virus foreign to the cow. Our experiments have been with fowl pox, turkey pox, herpes simplex, transmissible gastroenteritis of swine, and swine cholera. It is noteworthy that viral pneumonia in calves is self-limiting in herds, apparently through colostrum transmission. Thus, there is a natural paradigm for viral protection by this route as well as for bacterial diseases. In addition to bacterial and viral antigens, we are investigating other disease-producing agents. The metazoan parasites of animals and the pollen allergens of man are as subject to these phenomena as are the usual pathogens, and a program of testing antibodies to them has been set up. The range of antigenic material to which the cow's udder will respond seems limitless.

As mentioned before, the availability of this antibody to the calf after 72 hours of life has been questioned. We have found that absorption does occur not only after the early period of infancy but in the half-grown and the adult state. For these experiments we used colostrum and milk in which high titers to Salmonella pullorum had been induced. Two 5-month-old calves, weaned from milk and with fully functional rumens, were each fed 6 liters of 1 to 1,000 titer milk and their blood promptly went from negative to positive in response to the agglutination test.

Other species are similarly able to absorb this material. In an experiment upon ourselves and our graduate students, 5 adult men who were negative to the test for Salmonella pullorum showed positive titers up to 1 to 10 dilutions within several days after consumption of 1 liter per day of 1 to 1,000 titer milk. After 2 feedings of the milk, 2 adult pigs weighing 100 kilograms apiece reacted similarly with a positive test. Young and adult chickens, a species in which Salmonella pullorum is pathogenic, have shifted from negative to positive after feedings of immune milk. In guinea pigs, the ingestion of 2 gm. per kilogram of the isolated gamma globulin resulted in the appearance of agglutinating antibodies in the blood. Returns were similar with rabbits using doses of 2 gm. per kilogram.

To test the efficacy of these antibodies as transferred across species lines, an experiment was performed on chicks. They were challenged intracardially and intraperitoneally with a virulent strain of Salmonella pullorum. For the two days prior to inoculation, half were fed with colostrum in which a high titer to this organism had been evoked by vaccination of the cow, and the other half of the group were fed a control colostrum not containing the specific antibody. All chicks died of the infection; those that were unprotected died significantly earlier.

The antibodies produced in the cow's udder show the same lability characteristic of all gamma globulins. In order to handle them more effectively in experimental situations and with the idea of making them available in some form other than in fresh raw milk, we have developed processing methods which avoid the denaturization of these active bodies. From the colostrum, where the gamma globulin fraction may equal 20 per cent of the entire volume, a preparation of the isolated fraction may be accomplished by clearing the substance of fat and casein and then precipitating the gamma globulin with cold alcohol. The product so obtained is easily lyophilized and the subsequent white powder has shown

excellent retention of its activity when kept refrigerated. Effective pasteurization of the high titer milk has been accomplished by adequate temperature control. In addition, drying procedures have been worked out which retain all or most of the activity. The resulting product keeps well at room temperature.

The immunity which is transferred by this milk is passive immunity. In contradistinction to active immunity which requires a disease process and allergic inflammation[6] for its maintenance, the biologic cost of passive immunity is nil. Such immunity is, however, temporary and must be maintained by addition from an external source.

SUMMARY

The fact that the cow's udder is a remarkable producer of immune bodies is presented. The results of our experiments show that specific antibodies to a wide range of disease antigens may be evoked by proper vaccination of the cow and utilized when man and other species ingest the milk.

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In summarizing a series of observations and experiments extending over a number of years, we wish to acknowledge the aid of many collaborators who include: R. M. Porter, R. A. Good, M. Sarwar, I. D. Porterfield, P. J. Dziuk, L. W. Wannamaker, H. C. Pierce, E. L. Lassila, H. Struss, J. J. Bittner, M. M. Hirsch, and A. O. Dahl.

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Organic laryngeal disease often results from spastic misuse of the voice, according to George B. Ferguson, M.D., Durham, N. C. Some types of occupation as well as specific personality types tend to produce spastic vocal disorders and ultimate vocal cord damage.

When a high-geared nervous person with rapid, explosive, continuous speech is placed in a job which fosters tension, trouble is apt to occur. The politician, teacher, minister, high-pressure salesman, and harried mother are all susceptible. Any patient with chronic or frequently recurring laryngitis should be suspected of having vocal trauma.

Acute vocal traumatic lesions come on suddenly and usually subside promptly. Submucous hemorrhage of the vocal cords is not uncommon in the enthusiastic sports fan. Acute traumatic laryngitis may be induced by similar vocal indiscretions. Lesions of this type usually clear with brief periods of vocal rest and rarely leave any permanent damage.

Some chronic organic laryngeal disorders appear to be definitely associated with spastic or hyperfunctional disorders. Vocal nodules occur most frequently in workers who must speak above noise. The prevention and sometimes the cure of this lesion seem to lie in simple reduction of voice use. Insulation and sound-proofing of industrial plants often will allow reduction in the use of the voice. Patients must learn to speak as little as possible and to move closer when speaking to another person.

Contact ulcer is less frequent than vocal nodule and presents a complicated problem. The patient with this lesion usually exhibits severe nervous tension and often has psychiatric troubles. The condition is perichondritis of the vocal process of the arytenoids. The patient with contact ulcer, often tense and continually active, is best treated by very careful vocal reeducation.

George B. Ferguson: Laryngoscope 65:327-336, 1955.

Reflections on Student Health Work

WARREN E. FORSYTHE, M.D.

Ann Arbor, Michigan

Obviously no experience can be gained in the technic of retiring during forty years in a career. How to cap a professional life in this challenging and complicated field seems to call for that priceless virtue, wisdom.

The wisdom of these particular reflections on my part is certainly more to be questioned than the extent of the courtesy extended to me today. I have attempted no complete treatment nor comparisons.

HISTORY AND DEVELOPMENT

We are aware of the many papers, surveys, reports, and developments of programs, particularly within this century, which make up a considerable history of student health work here and abroad. This is a development with which many have been identified and, I am sure, with great satisfaction. Attention to student health has become a recognized, established, somewhat standardized, and important activity in our colleges and universities.

In this connection few have failed to express to Amherst and to Dr. Edward Hitchcock highest admiration in recognition of their pioneer leadership in the 1850's.[1] The award to Amherst College by this association at its thirteenth annual meeting in 1932 was such recognition. Harvard and other private colleges established infirmaries at the end of the last century and Reinhardt started a more complete clinical service at California in 1906. We have recently been reminded of Cornell's bout with typhoid in 1903.

The early integration of our special approach with physical education, the gymnastic period, is well known.[2] Some physicians who fostered physical education were: Sargent, Anderson, Raycroft, McKenzie, Reinhardt, and Leonard who trained Williams, Reed, the Fauvers, Nichols, Nash, Moulton, Morrison, Thomas Wood, and others of the Oberlin group.

Without records for quotation but, as I recall it, about the year 1914, I received from George H. Simmons, who was then editor of the *Journal of the American Medical Association,* distinct disapproval of the clinical features of this new activity. Probably the black beast, socialized medicine, was blacker then than now.

The part which Dr. Thomas A. Storey played in this field has impressed me. I think of his sustained early interest, activity, ability in editorial work, his critical analyses, his capacity for organization and interesting other people, his ability to express ideas, his defense of the word "hygiene" and his ability to subdivide it.

In 1913, he led an International Conference on School Hygiene in Buffalo and edited the Transactions.[3] Volume 5 reports a symposium on "Health Supervision of College and University Students" with participation by Phillips, Robertson, Raycroft, Abott, McCastline, and Reinhardt.

Around 1920, Drs. Storey and William F. Snow secured approval for the use of unspent war funds of the United States Interdepartmental Social Hygiene Board to promote student health work primarily in our teacher training colleges.[4] Over the years 1919 to 1922, $700,000 were allocated to 40 colleges in 29 states. Many programs got their start from the directions and financial assistance of that agency as directed by Dr. Storey.

As an activity of that board, a committee of 50 college presidents was organized to promote the extension of these programs. By personal visits the then most complete and accurate study was recorded of this interest in colleges and was edited by Storey.[5] These 122 pages are full of present day interest.

Dr. Storey practically wrote the early constitution, by-laws, and setup of this organization. He originated, organized, directed, and wrote most of the report for the First National Conference on College Hygiene. He established and directed at Stanford an integrated School of Hygiene and Physical Education to include health teaching, health service, and athletics. In 1935, he wrote a textbook on The Principles of Hygiene.

WARREN E. FORSYTHE, *a 1913 graduate of the University of Michigan Medical School, is professor of hygiene and public health and director of health service at the University of Michigan.*

Presented at the 1955 annual meeting of the American College Health Association at Colorado Springs, April 28 through 30.

On March 4, 1920, Dr. John Sundwall called a well-attended meeting in Chicago which established our organization. Minutes of that meeting are available in the Proceedings of our tenth annual meeting. Ideas of opposition are not recorded, based upon the opinion that it would be just another organization to support and promote. Perhaps some of us agree that such opposition should have prevailed with regard to many other organizations of specialized interests that have been created since that date. It was agreed then that we would promote limited meetings of interested persons and let time and experience determine the size and scope of our project. I think we agree that Dr. Sundwall was wise in calling that meeting. Several of us knew of his good judgment in promoting student health in relation to health education at all levels. His Division of Hygiene and Public Health, organized about 1921 at the University of Michigan, combined all of these interests including physical education.

In 1924, Mock and associates[6] reported a good study through the Interfraternity Council, and in 1932, an exhaustive study in 6 universities by the Committee on Costs of Medical Care Number 19 was reported by Griswold and Spicer. We know the report of Diehl and Shepard for the Youth Commission in 1939[7] concerning the health of college students.

In 1941 and 1942, Legge[8] of California and Raycroft[9] of Princeton gave us their mature reflections upon many years of pioneer experience. As published in The Journal-Lancet, they are excellent short summaries of our history, program, leaders, and ideals.

HEALTH PROGRAM

The term Health Program as applied to our colleges is proper and pertinent. Regardless of the actual health situation, the term suggests planned or consciously operated activities for this purpose. Courses of instruction and activities which have some incidental and secondary broad health connotations and those for professional preparation might justifiably be included as part of a health program no matter how scattered and uncoordinated. Probably no college president would admit that he did not have a health program, however limited in scope or in his attention and support.

While a few pioneer programs were remarkably complete, we are well aware of present day variations in content, application, and support. Our programs might be judged remarkably uniform in view of institutional differences in needs, policies, resources, and personnel.

Whether one is impressed by the uniformity or the variation in our programs, this audience probably agrees that after these decades of free-wheeling more standardization is needed. Definitions, diagnoses, limitations of terms and data that make up our reports are certainly needed to make possible evaluations within and between institutions.

Relative emphasis on health education versus personal medical care are extremes in which programs may vary. Certainly local circumstantial variations exist even in program features accepted as basic. The relative advantages of standardization or variation in programs might justify a symposium discussion by this group to consider standardization and definition of many terms and features of our programs and reports. Perhaps steps might be taken to obtain from our presidents a breakdown of the college objectives to the end that our departments may better direct or integrate their programs. To what extent are our objectives the primary purposes of the institutions? A statement of more specific principles might be requested as guides in operation. To this end, an effort might be made to quiz our presidents on their understanding of the conclusions of our national conferences.

For our departments, answers to many questions might be agreed upon. What is the desirable relation of the established health service to administration, a coordinator, health instruction, R.O.T.C. service, environmental health questions, faculty and employee health, care of athletes, student admissions, and counseling? What is to be understood by terms in our reports such as: clinic, clinic call or visit, enrollment entitled to service, patients, deaths, examinations, operations, and bases upon which rates are determined?

How are costs determined – gross or net, sources of credits, uses made of other departmental budgets, totals and breakdown, and so on? What services are included for emergencies, for elective conditions, during vacations, for students out of residence, irregular enrollment status, and guests? What use is to be made of existing insurance coverage?

In such a conference some attention might be given to a philosophic elaboration on the words "health" and "service."

PROGRAM ITEMS

1. *Health education.* Brief comment on some items common to these programs may be in order, and in my opinion health education heads the list. No one could have been alert to the problem of education in general during the past

few decades without appreciation of the growing confusion concerning meanings, methods, objectives, achievements, and definitions of the process of education at all levels. The tremendously significant results of the recent application of the scientific method to the problem of human behavior seems to have contributed to this change.

Modern students of education have certainly made it difficult for those of the old school who assumed that students wanted to learn. Previously accepted methods of oracular transmission of information, facts, and opinions from on high meet raised eyebrows. Solutions of student problems, creation of obscure, individual, and receptive attitudes seem to be prerequisites to the learning situation, but the reproduction of information still seems to be the only practical means of evaluation for promotion in the academic situation and otherwise.

Some persons still think that information and facts play an important part in intelligent conduct, and lectures still are much used in higher education.

Formal instruction. Health education required under a variety of titles has a long but unenviable record in the college curriculum. Jackson's lectures at Harvard in 1818 are noted. For a variety of reasons we know that such courses have not done well in most places. We are equally aware that they have been a success in some colleges and that in our conferences and meetings required courses are always advised.

Required instruction. I am sufficiently old fashioned to think that mature leaders of experience should be in a position to decide some things that are fundamental and, in the process of education, health courses should be required. However administered, I am quite sure that the physician cannot be depended upon to give such courses generally, but Beard at Illinois and others have done well with sustained programs.

We recently sounded the requiem for a thirty-five year program of 6 one-hour lectures as a freshman no-credit requirement at Michigan. Upon the basis of student opinion and our own evaluations, they were continued many years under unfavorable conditions, but student attitudes and other situations of recent years caused us to advise that such instruction be required only in regular credit course work. This is not yet in effect.

Informal education. Most of us probably agree with the modern concept that health learning, at least, is most effective individually or in small groups when identified with a particular patient problem. In consideration of the numbers benefited and the scope of subject matter, this method of learning is, of course, most inefficient and expensive, certainly in terms of rare physician hours.

A recent article in the United States Public Health Reports by Skinner and Derryberry[10] deals admirably with this opportunity in the clinic. Many other avenues of informal health education which are available to our colleges challenge our initiative, imagination, and enthusiasm. The service of a health educator to promote and coordinate such enterprises would seem wise.

2. *Environmental health.* We are probably less identified now, by title at least, as the college health officer than before the development of the clinical approach to public health. This change of emphasis in public health, the development of specialists, the nonmedical sanitarian, variations of administration in the colleges, and so forth, have possibly retarded or confused our responsibility for attention to student health as determined by environmental conditions.

Dr. Legge, as university physician at California, was made completely responsible for public health early in his career and given an adequate staff to cover several campuses which have been developed to include radiation and industrial aspects. More recently Dr. Boynton of the University of Minnesota Health Service has added a significant staff. Only by assumption has the Health Service at the University of Michigan had jurisdiction in these areas, with one staff sanitarian on a full-time basis during the past five years. He renders assistance to other campus agencies and covers specific situations, but the whole question at Michigan is under consideration at present.

Food handlers and other nonstudent associates present health problems in the environment and the clinic.

3. *Physical education and recreation.* Historically, physical education is the father of school health at all levels and our associations have been close. The more recent emphasis upon athletic contests and our clinical emphasis have raised questions. In spite of the attitudes of medical people and others, I have long maintained that properly controlled physical exercise and game participation promote health. Certainly major cooperation of these activities with ours is very important. The relationship of the Health Service and intercollegiate athletics at Michigan is about as good as can be expected. I am reminded of a college president who believed intercollegiate athletics were practically outside the control of administrative officers.

Aside from physical activity, I am not aware of much that our health agencies have done to promote recreation in this day of emphasis upon *stress* in substandard health.

4. *Personal clinical feature.* We probably agree that the present leading public health problems require an individual personal clinical approach. Hence, this approach to the health of college students is wholly justified. The responsibility of the college to provide this purely clinical medical service is more open to question. In his annual report of 1920, President Butler of Columbia stated, "Mental and physical health come before either textbooks or laboratories as educational instrumentalities." A good A.M.A. study report in 1936[11] expressed disapproval of this belief, indicating that the college should meet its primary educational and protective functions. The point of view of the medical profession at that time on this subject is well presented by that report.

Regardless of opinions on student health, our colleges are at present, and for good reasons, practically forced to assume some responsibilities for giving medical care. The extent of care varies over a wide range and depends upon local conditions and administrative policy.

A situation concerning the use of our health clinics, which upon occasion I have mentioned to our students, relates to the social problem of obtaining good modern medical care. Surely by actual use, these future leading citizens should determine whether or not they want medical services at least available to them in an organized plan. Will they not want later for themselves and their families medical services easily available, centralized, planned, and modern, upon some basis of distributed cost? Will they not realize that many persons and facilities are involved today in giving good medical attention and appreciate the wisdom of using these highly trained persons and expensive accessories efficiently?

Some general questions. With the wide variations in size, facilities, and so forth, in our institutions, a discussion would be difficult of even a few of the many related questions which have concerned us in our meetings, national conferences, many papers, and reports.

In our larger universities, we have endless problems because of limitations imposed by irregular service for faculty, employees, part-time students, invited high school groups, convention members, visitors, student families, former students, our own staff members, and summer session work shops. At Michigan, alas, we have yet to secure evidence of freedom from active tuberculosis in the faculty and most employees.

Local facilities and conditions are known to cause variations in medical service available to even regularly enrolled full-time students. Very unusual resources would be required to meet an ideal of positive physical and mental constructive service in a broad view of preparing these selected young people. At present most of us would, of course, be happy if, financially, each student could be assured that his present educational plans would not be interrupted for want of medical care. The plan in effect at Michigan has, from the first, largely been able to meet this problem and provide medical care without consideration of the student's financial status. For many years we have had an optional identified health fee for *part-time* students only. Reduced charges are made for some services, mainly elective, and use is made of sickness insurance already covering the student. We have attempted no general insurance plan.

A staff is also affected by local conditions, and the part-time use of those in near-by training programs has many advantages, particularly in special services. Of course the strength of our services depends upon full-time people actuated by the spirit of broad sustained service which should characterize such work. These persons should represent the student's medical home base and advise him in such matters as securing and interpreting the attention of specialists. Special staff assignments by classes or groups have much advantage.

Features selected. A determination of health as a condition for admission is a feature long recognized as basic to our programs of industry, employment, and so forth.

With increased numbers of students, problems of enrollment, and other pressures, the problem of completing health examinations increases. Except where an extra staff can be mobilized for this purpose, it would seem logical to require the student upon admission to present a uniform minimum record of data from any physician showing that he is physically fit to enter the institutional program. With that information, the college could develop its own observations and program consistent with its special objectives.

Follow-up. The follow-up of entrance examination findings offers, of course, preventive and constructive opportunities. Technics, thoroughness, and policies concerning follow-ups vary greatly. *Later examinations* annually, or otherwise, are well recognized as valid in the attack upon the problems of personal health. As we know, their effective realization requires sustained time of physicians whose tolerance of

routine and desirable attitudes are hard to maintain. Years ago I gave up an attempt at enforcing required annual examinations of all students. Difficulties of enforcement, limited new findings, and crowded staff time seemed to result in unfavorable student attitudes. Minnesota has developed such examinations gradually and with encouraging results. Let's keep this requirement on the calendar.

Perhaps we should promote more practical and less formal health conferences based upon a review of records, student interest, indicated observations, and fewer routine procedures for this feature of our work.

Outpatient clinics. Our clinics should try to find answers to many problems which will arise as this plan of service is used more in our general populations. A few such problems are:

Administration in general.

Restriction of service to those who are eligible, recognizing the fact that there may be cases of assumed names.

Reaction to dispensing of stock drugs by the physician in the office rather than writing a prescription.

The question of abuse of clinic time by patients who come in for insignificant and trivial conditions.

Requests by others for information obtained by the clinic.

Responsibility for follow-up of noncontagious conditions.

Telling patients about their conditions, particularly suspected malignancy, to insure proper attention for follow-up.

Service out of hours.

Determination of emergencies versus elective conditions where free service is limited to the former.

Determination of who are tuberculosis contacts.

Assignment to physicians where differences in popularity exist.

The extent to which appointment systems should be used in the general clinic where people are encouraged to come in at any time.

The insistence upon payments by insurance companies for service otherwise free to the patient.

The completion of long involved forms for insurance, transfers, and employment purposes.

Service during vacation or other times when the patient is not entitled to service. Mail requests for prescriptions formerly given.

Arrangements whereby the same doctor sees the same patient at subsequent visits.

Conditions for which notices should be sent to parents or relatives.

"Excuses" for failure to attend classes or meet other obligations.

In referring patients to auxiliary services as, for instance, is the x-ray man a consultant or technician in preparing plates to be interpreted by the referring physician?

Order in which patients are seen.

Filling prescriptions or other requests of students for physicians not connected with the department.

Arrangements for the delivery of patients' records to the doctors without the possibility of the records being seen by the patients.

Terms to indicate the varying types of examinations requested.

Extent to which services may be delegated upon standing orders, as for treatment of colds.

Possibilities in use of IBM cards in routine records.

Applying to physicians in particular.

Keeping hours.

Recording diagnoses and notes such as can be read and counted in accurate reports.

A uniformity of terms to be used in listing patients under diagnoses and other headings.

Limited use by physicians of laboratory determinations, x-ray examinations, and specialists.

Legibility and length of notes on clinic cards.

Restriction concerning use of special, proprietary drugs.

For the hospital in particular.

The liberal use of easily accessible, free bed care without developing in patients a resistance to the idea of entering the department for fear of being kept in bed.

Determination of the number of visitors allowed and visiting hours.

Hours for physician rounds on bed patients.

Mental hygiene. I am in sympathy with the authoritative opinion that "Mental illness is one of the most challenging and baffling problems with which man must wrestle today," and another "To harmonize the pressures exerted by society and by the individual drives is the greatest single problem of human lives." The long range view is optimistic to me because the methods of science are being focused upon problems of human behavior, so long dominated by methods of nonscience, and asocial considerations of technology.

Dana Farnsworth and others have certainly been pouring it on so far as our work is concerned. I am sure we would be pleased if we had even the staff to handle these almost emergency problem cases as they arise without visions of wider constructive service for social adjustment. Possible prevention by seeking and attacking stress producing campus situations has long appealed to me. Does pressure for selection in campus organizations, pressure for grades, or anything else produce problems in our field? If such could be proved, I suppose the point might well be made that such problems are desirable in the process of social maturation. Surely some answers in this area are being developed in our clinics for wider application.

Bed care. Easily available beds in close proximity to the general clinic are, of course, basic to a medical care program. In our situation the range of bed occupation presents a real problem. Necessary staff maintenance with minimum waste during periods of little use is difficult in some of our infirmaries.

The control of student visitors and the frequent reluctance of students to be advisedly confined for fear of missing other appointments may

make the Health Service less popular, particularly with girls.

Room calls. The provision of an available number of physicians to call at student rooms varies among our departments. Distances make these calls a real difficulty, but, where reasonably possible, its refusal is hard for students to understand. Physicians continue to call on students at Michigan with increasing charges for such trips. Students seem to be realizing the advantages of coming to the department to which a physician may be called at nights and other off hours.

Many items of medical service in our programs such as the importance of refractions, required routine tetanus immunizations, and so forth, could be discussed.

PROBLEMS

In addition to problems already suggested, a few of many others are:

Opportunities for investigations dignified by the term research, of course, always confront us. Who is in better position to evaluate cough remedies?

Contacts with foundations and other philanthropic organizations for support in new lines of work.

Basic sources of student criticism.

Critical evaluations and improvements in the entire line of work.

Anticipated increasing numbers of students whose registration and service control become more complicated.

Availability of our records in the total program of counseling and guidance.

Consideration of overlapping functions of academic departments of Psychology and our departments of Mental Hygiene.

The way in which our departments are considered, whether as service units or as contributors to the primary purposes of the institution.

The training of future directors.

SUMMARY

In reflection, words fail me in expressing my opinion of the importance and significance of the work being done. The words of many others could be marshalled at this point, but a few quotations may suggest the spirit of the base upon which this work rests.

1. From the classics, I was impressed by a translation from Cicero's oration for Quintus Ligarius, "In nothing do men more nearly approach the gods than in giving health to others."

2. From Simmons, then dean of the School of Public Health at Harvard, "America's great strength is based upon just one thing – the health of her men, women, and children."

3. And last, but not least, from our own Dana Farnsworth's reference "our opportunity to share with these potentially important people the tremendously important experience of adjustment for social success, happiness, and service."

I am less concerned about words than questions of propriety in reflections upon myself in this connection, but I am pleased that most of my professional work has been in this field and I cherish the many friendships I have made in our organization and in related activities.

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Facilities of the State Hospital at Jamestown, North Dakota

JOHN G. FREEMAN, M.D.
Jamestown, North Dakota

THE STATE HOSPITAL at Jamestown was authorized by the Dakota Territorial Legislature to relieve the Territorial Hospital at Yankton. It was officially opened May 1, 1885, and is celebrating its seventieth anniversary by holding "open house" May 6 and 7, 1955. Past records show a fairly steady growth at an average rate of 30 beds per year. The present population is slightly over 2,000. Based upon the experience of other states, we will soon require 3,200 beds if the population of North Dakota remains constant.[1]

For years organizations in the state have been interested in the problems of mental health and mental illness. Prior to 1936, the medical staff of the State Hospital helped conduct mental hygiene clinics. The members of the 1953 legislature were responsible for initiating the present program and for setting in motion a series of events which led to increased activity and interest in the hospital, its problems, and its facilities.

The attitudes of many persons, including patients, relatives, and officials throughout the state have been rapidly changing. As a result, the number of persons being committed or seeking voluntary admission to the hospital is increasing at a phenomenal rate, making it even more difficult to find time for reorganizing and improving treatment programs and other services and facilities.

In the ten months of this biennium, we have already admitted more patients than in the first fifteen months of the last biennium. The hospital is nearly one-third overcrowded.[2] Unless releases occur rapidly enough to make room for entrances, a waiting list will be necessary.

On admission to the hospital, the patient and whoever accompanies him are directed to the admission room. No patient, voluntary or otherwise, is yet admitted to the hospital until seen by a member of the physician staff. Admittance in the same manner as that employed in the ordinary community hospital would be better, but we find that a brief physician's record of the patient's condition at the time he enters the hospital is necessary. At this time, one of the hospital supervisors lists money and valuables and places them for safekeeping in the hospital office or vault. Storage space, even bedside space, is so scarce in our overcrowded hospital that the supervisor tries to send home with relatives all except extremely necessary possessions. While the patient is being taken to the receiving unit, a member of the social service department interviews the patient's relatives, friends, or sheriff, obtaining information regarding events leading up to and the reasons for admission. Later, social service may be requested to secure more detailed information on specific items. Either a social worker or a supervisor may suggest to relatives additional items of clothing needed, appropriate amounts of spending money, and hospital policies governing visiting hours, mail, gifts, and so forth.

When the patient arrives at the receiving unit, his clothing is listed and inspected for overlooked valuables. A bath and shampoo are given and he is carefully inspected for bruises, scars, skin rashes, or other lesions. Except in emergency situations, the routine laboratory procedures, red blood count, white blood count, differential count, Wassermann test, urinalysis, chest roentgenogram, and dental examinations are done by scheduled appointment during the first few days in the hospital. Dentures, if required, are provided at cost. The physical, neurologic, and psychiatric examinations are completed; a working diagnosis is established, and a treatment program is outlined on the day of admission or the following day. With the exception of those patients who are committed in terminal condition, emergency situations are infrequent and are usually represented by severe delirium tremens, heart failure, pneumonia, or diabetic comas. Patients in acute conditions because of attempted suicide

JOHN G. FREEMAN, *a 1944 graduate of the University of Minnesota, is clinical director of the State Hospital at Jamestown, North Dakota.*

Read at the annual meeting of the North Dakota State Medical Association, Bismarck, North Dakota, April 30 to May 3, 1955.

and patients in states of exhaustion are quite rare. The director of the medical-surgical department and specialists in the city of Jamestown are available to the psychiatric staff for consultation.

We desire as far as possible to treat and discharge the new patient from the receiving unit or its neighboring convalescent unit. This will be more easily accomplished when the new 200-bed admission and receiving building is completed in 1956. At the present time, many patients must be transferred from the admission unit because of lack of beds. We must then mollify dissatisfied or bewildered relatives who consider the transfer as possible evidence that we consider the patient untreatable. The patient's own needs or behavior sometimes requires transfer to other units. He may be transferred to the medical-surgical unit for special diet, surgery, or for special bedside medical care. A patient receiving prolonged individual or group psychotherapy is transferred to a ward where he can at the same time participate in a hospital industry. A very disturbed patient should not be kept on the admission unit where his behavior might retard the progress of others.

Special laboratory or x-ray examinations, as indicated, may be ordered any time after admission. On request, the psychology department gives examinations ranging from an I.Q. determination to a complete battery of tests designed to evaluate personality organization and current defense mechanisms. A member of the social service department interviews the patient to obtain information and to offer services in many questions regarding financial problems such as insurance benefits, payment of taxes, support of spouse or children, leave of absence from the job, collection of wages, and rerouting social security checks. Assistance is given in matters pertaining to location of possessions, contacting relatives, obtaining new employment upon release, continuing education through correspondence courses, and in a myriad of other requests. The Stutsman County Veterans Service officer calls on patients who are veterans to assist in pensions, compensation, and applications for transfer to a Veterans Administration Hospital. The hospital chaplain or a visiting Catholic chaplain visits patients to offer services and to help contact the minister in the patient's home parish. As soon as the patient's physical and mental condition is satisfactory, the patient placement officer assigns work in the hospital in accordance with the patient's needs, if prescribed, or in accordance with the hospital's needs. Most mental hospital patients are physically able and can assist in such daily responsibilities as cleaning, making beds, working in the electrical shop, carpenter shop, butcher shop, or other hospital industries.

Entertainment is provided by the recreational department which also conducts prescribed recreational therapy designed to fit the needs of the patient. The occupational therapist conducts prescribed occupational activity. A beautician visits the ward, or the patient may be allowed to go to the beauty shop. Volunteers visit the ward to assist in writing letters, visiting, conducting entertainment, or bringing the library bookmobile to those who cannot go to the library. The birthday committee arranges with organizations throughout the state to give a birthday party every month for those patients whose birthday occurs in that month. Average attendance is 70 per month, plus gifts for about 60 who cannot attend.

The treatment program for a patient seldom consists of only one process. Since the combinations are almost impossible to describe, each will be discussed separately:

Insulin therapy.[3] Coma and subcoma insulin therapy were discovered by Manfred Sakel in Austria about 1935 when he was using insulin to alleviate withdrawal symptoms in drug addicts, and later to quiet excited schizophrenics. In those days, insulin was a crude, poorly standardized product; as a result some patients received overdoses and became comatose. He recognized that this undesirable side effect was beneficial to some patients. Meduna and other physicians were deliberately producing convulsions with toxic substances such as Metrazol. Insulin coma therapy is now designed to produce about fifty hours of deep coma in the treatment of schizophrenia. Thorazine, by its action on the hypothalamus, may produce a similar result in a safer manner. Insulin therapy was first used in Jamestown in 1938.

Electroconvulsive therapy. As results of Sakel's use of insulin and Meduna's reports on Metrazol convulsions, Cerletti[4] in Italy in 1937, discovered a method for using electricity to produce safe controlled seizures while investigating the possible effect of convulsions on brain tissue of animals. Electroconvulsive therapy is principally used in treatment of the manic-depressive and involutional depressions. Convulsive therapy was started in Jamestown with the use of Metrazol in 1939 and was replaced by electroshock in 1940.

Group and individual psychotherapy. The only psychotherapy available prior to 1954 was that which could be done by the understaffed

psychiatric department. Group and individual psychotherapy was started in 1954 by members of the newly organized psychology staff under the supervision of members of the psychiatric staff. Over 50 patients are now in individual psychotherapy, and over 120 patients are in group psychotherapy which ranges in intensity and depth from superficial to intensive.

Hydrotherapy. Stimulating and sedative effects derived from the use of water have been used in treatment of psychiatric illnesses for centuries. Hydrotherapy, in spite of antiquated equipment, is put into use each day at the State Hospital.

Occupational, recreational, and industrial therapy. This department has existed in one form or another since the beginning of the hospital when wives of staff members participated. Occupational therapy is "any activity, mental or physical, definitely prescribed and guided for the distinct purpose of contributing to, and hastening recovery from disease or injury." This department is still unorganized, but its components are providing useful services in therapy as well as carrying out responsibilities for entertainment.

Drug therapy. In the history of psychiatry, such medications as hormones, extracts, sedatives, and vitamins have periodically been introduced, waxed, waned, and disappeared. Thorazine and reserpine derivatives are the medications of current interest and investigation.

Psychosurgery.[5] The first destructive operation performed on an otherwise intact brain in hope of relieving mental symptoms occurred in 1890. The present psychosurgery technics were initiated by Egaz Moniz of Portugal in 1935. No psychosurgical procedures have been done at this hospital. However, agreement with a neurosurgical consultant has been made, and operations will take place in the near future.

Program for alcoholism. A patient with a problem of alcoholism is hospitalized about five weeks, during which time he is first treated for acute alcoholism or delirium tremens, if present, and then is exposed to the principles of Alcoholics Anonymous. Efforts are made to secure immediate employment, and he is introduced to an A.A. group in the community prior to release. The director of the North Dakota Commission on Alcoholism visits the hospital two or three days every second week to interview and counsel alcoholic patients and arrange for community A.A. contacts. Results of this five-week program appear to be no better nor any worse than longer programs elsewhere.

Physiotherapy. A physiotherapist has been employed to aid in the treatment of physical ailments which may not be a proper responsibility of a psychiatric hospital, but which often tend to be principal reasons for commitment, such as coexisting birth injury disabilities, residuals of a cerebrovascular accident, paralysis agitans, postfracture rehabilitation, and reambulation of patients who may have been neglected at bedrest for months prior to commitment.

Outpatient department. The outpatient department has been located in the Medical Center building at the State Hospital since April 1954. Referrals to the clinic for mental or emotional problems come from many sources, such as the patient himself, family physicians, welfare agencies, teachers, lawyers, ministers, public health nurses, and juvenile commissioners. Patients of all ages from preschool to nearly 90 have been registered. Diagnosis, recommendations, or treatment services are available, ranging from a brief discussion of a relatively simple problem to extensive examinations followed by a long-term treatment program. Diagnosis only is seldom requested except by certain officials or agencies. Typical questions are: Is this child mentally retarded? Is this person competent? Was this person mentally ill? Recommendations often requested include questions such as: How should we handle this problem? What plans should be made for the future? Is it necessary for my relative to enter the hospital? Treatment facilities range from outpatient electroshock in carefully selected cases to group and individual psychotherapy with the patient or members of the family. We prefer to have the individual, not a friend nor an agency, make an appointment for examination by writing to: Outpatient Department, State Hospital (or Box 476), Jamestown, North Dakota.

Length of hospitalization. The usual alcoholic patient is released from the hospital five weeks after admission. The usual depressed patient, treated with electroshock therapy, is released after six to twelve weeks of treatment and observation. The schizophrenic patient with considerable emotional display is often released in about the same length of time. Patients treated with insulin are usually hospitalized three to eight months. Many aged patients are admitted because of depression and respond like other depressed patients to electroshock therapy, so that they are able to return home in six to eight weeks. Aged patients with senile or arteriosclerotic confusion and disorientation often improve to a very surprising degree after two to three months of hospitalization where they are free of family conflict and responsibilities. This is also true of a number of those hospitalized because

of confusion after cerebrovascular accidents. Because of lack of really adequate histories, we are not certain how many elderly people are admitted to the hospital because of barbiturate confusion. Even small amounts of barbiturates often cause confusion in elderly and often somewhat dehydrated persons. This confusion often disappears after two or three months of freedom from such drugs. The elderly person may still be somewhat forgetful, but he usually is able to return to his former surroundings when his confusion disappears.

The facts are that most patients who are committed to the hospital are released to return to their home communities. Every month 90 patients enter the hospital. Each month about 10 persons die in the hospital and about 80 are released on parole or discharge. Of those released, 80 per cent never enter the hospital again. The other 20 per cent return to the hospital for a second time and are released. A very small number enter the hospital more than twice, and these are usually patients who suffer from recurring depressions.

Staff review. Only the more difficult case problems are reviewed by the entire staff after admission examinations are completed. A few patients who are not responding as expected to the outlined treatment program are presented for staff recommendations. All patients who are released from the hospital are first interviewed by the entire staff.

Coffee shop. The coffee shop has recently been doubled in size and resembles the small cafe, soda fountain, or drug store in any sizable community. (The State Hospital itself is the sixteenth largest community in the state in terms of population.) Snacks, lunches, hot soups, ice cream concoctions, sandwiches, and coffee are available for patients, relatives, friends, and outpatients. Items not provided by the hospital's general supply, such as cosmetics and other beauty aids, pipe and tobacco items, magazines, greeting cards, and occupational therapy products are also for sale.

Other departments and facilities. In the preceding paragraphs, only partial services of many departments were mentioned. These and others include the following: psychology department—testing, psychotherapy, and research; chaplain department—religious instruction, counseling, reorientation, and home parish contact; dental department—examination, prophylaxis, and dentures; medical-surgical service – consultation, medical or surgical procedures, special laboratory, x-ray, physiotherapy, and related procedures; O-R-I department—occupational therapy, recreational therapy and entertainment, arts, crafts, and shop work; psychiatric department—insulin, electroconvulsive therapy, group and individual psychotherapy, drug therapy, and management of the psychotherapeutic program; social service department—finances, education, and social services; patient placement service—work in hospital industries, such as farm, garden, dairy, kitchen, butcher shop, cafeteria, housekeeping, store and warehouse, garage, engineering, and maintenance shops; beauty shop; barber shop; library; Alcoholics Anonymous; and business office.

SUMMARY

In spite of the problems involved in treating such a great number of patients, we feel that the citizens of the state can feel confident that the newly admitted patient is receiving good psychiatric care, and, in some cases, care that cannot be obtained elsewhere except by very wealthy persons. To receive this care, however, I regret to say that the patient must put up with a number of unpleasant experiences, such as overcrowding, poor plumbing, lack of many conveniences, little personal attention, loss of many privileges, and less than satisfactory food service. These situations will be corrected as rapidly as they can be financed by the people of the state. The prospective patient would be helped if he were informed that, to receive necessary treatment, he must temporarily bear with the difficulties involved in living in such a large hospital.

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Notes from a Medical Journey

Cape Town, South Africa

Dear Jay:

A month of feverish activity has gone by here in South Africa and in a few days we shall be back in Italy, joining Henry Taylor, Reuben Berman, and Paul Dudley White for the assault on the Island of Sardinia. Tomorrow we fly to Durban to lecture to the medical school and compress a week's conferences and visits into twenty-five hours. Thence to Johannesburg for over night and to emplane for twenty-four hours of steady flying to Athens to catch a glimpse of the Parthenon, and so to Rome.

From where I sit, the red tiled roofs of the white medical school buildings are at eye level all around me, the big block of the Groote Schuur Hospital is 200 yards up the slope, and right behind it rises the steep mass of Devil's Peak and Table Mountain. Over my shoulder, Table Bay gleams in the sun a couple of miles away, the waterline curving around to the brilliant white sands of Blouwbergstrand where we dined on Sunday evening. The Antarctic whaling fleet is moving into the harbor today, and I wish I could go down to the docks to greet the great "floating factories" on their return from many months beyond the end of the world. It is curious how the feeling persists that Cape Town is the "jumping-off place." Well, look at the map and you will see what I mean. Still, the people here find, as do people everywhere, that the world extends around them in all directions and they are in the center. And certainly nowhere else is the air more soft, the mountains more solid, the sea more blue, or the flowers more abundant. How good it must have seemed to the small band of Dutchmen who landed here just 300 years ago! And it seemed good, too, to the French Huguenots and the English settlers who came in successive waves.

Each lot took up new land and pushed further inland, alternately battling the natives and using them for labor. Incidentally, they contributed to the "colored" (half-caste) population, now numbering 300,000 people who form a transition between 8 or 10 million Bantu and 2½ million "Europeans." Add 100,000 or so Malays, originally brought in as cheap labor and a few Bushmen, who were here before the Bantu, and you have the population of the Union of South Africa.

A colossal problem of assimilation and integration, you would say, but the ruling Nationalist Party here wants none of it. "Apartheid" (complete segregation) is their creed, and to us this seems like trying to turn back the clock. Of course, we in America would rather forget our own history of Indian reservations, Negro segregation, and struggles between the states. But we have made tremendous progress toward our professed goal of equal rights and opportunities for all. Well, it is not for me to comment, though I cannot help but be astonished at the fantastic lengths to which "apartheid" goes and aspires in grim opposition to the general trend of the times in this fast-moving modern world. I suppose that nowhere in the Western World is the road ahead more obscure and beset with more political hazards than here.

Anyway, we go out daily to factory and office, sampling the Bantu, the colored, and the European, checking their diets and bloods, recording electrocardiograms and bodily dimensions. Professor J. F. Brock and Dr. Bronte Stewart organized everything beautifully with a "task force" of 14 people for this intensive research job. So cholesterol measurements and paper electrophoreses go on at top speed in the laboratory. We are running out of acetic anhydride and the slide rules are slippery with sweat as we calculate results. Dr. R. Singer of the anatomy department comes in to say that he finds no difference between Bantu and European in the architecture of their coronary arteries. Dr. B. Kaplan is measuring miles of ECG records, and Dr. Vogelpoel reports that only one myocardial infarction has been seen in a Bantu in thousands of patients in recent years in the hospital.

We have sought information everywhere, and the answer is always the same as Dr. J. Higginson reported recently in Johannesburg: "Bantu on their native diet have very little atherosclerosis and coronary heart disease is extremely rare among them." The colored people, whose diet and manner of life is between the Bantu and the European, are somewhere between the other two groups in the prevalence of coronary disease. And, most important, we find both diets and blood cholesterols correspond. Not only is the total serum cholesterol very low in the Bantu; the proportion of cholesterol in the beta lipoprotein is low. This is not a racial or genetic difference. Bantu who get a bit more fat in their diets have higher cholesterols, and there is a clear rise in Bantu and in colored cholesterol values with rise in income. The few Bantu who manage to approach the dietary habits of the lower stratum of Europeans here tend to have serum cholesterol values which correspond.

Dr. Bronte Stewart is already scribbling away at the first draft of a preliminary technical report on some of the findings, but the full story will take a long time to come. In the meantime, it is perfectly clear that the main findings here conform beautifully to the requirements of the theory that the dietary fat level is a major determinant for the blood cholesterol concentration, and especially that in the beta lipoprotein fraction, and hence for atherogenesis and coronary heart disease. Moreover, the reason for this action of dietary fat is becoming clear. Fats and fatty acids as such are insoluble in water and blood plasma and can only be trans-

ported in solution in the body when they are combined with cholesterol and proteins to form the water-soluble lipoproteins. The liver is always able to make the cholesterol to cover the fats to be transported in the blood and the needed protein moiety, only 5 to 8 per cent of the serum total protein, is readily at hand to complete the lipoprotein manufacture.

Well, more of this later. Now I must prepare a final lecture for the local Chemical Society tonight, and the field team is back with the morning's loot of blood and records. I begged off to write letters and calculate results. On the latter, I can tell the team that we have done very well in matching the ages of our subjects--the mean ages of the 3 groups are all within less than one year of 47. And Margaret can tell them that there are only 7 recent serums to repeat because of poor agreement between duplicates.

In a few hours we must pack. Our bathing suits were never near any of the inviting beaches; we never went fishing; and this letter was barely written. Still, we did climb Table Mountain one Sunday, and on another Sunday we picnicked by an idyllic stream high in the inland mountains. And we have delighted in wild flowers and domestic gardens and magnificent grapes and excellent white wine and the comings and goings of the "table cloth" of cloud on Table Mountain. Everyone has been most kind and friendly, and the scientific data fill our bag of good fortune to overflowing. But I still wish we could sit quietly by the sea for a few days. I'd probably sleep around the clock!

As ever,

Ancel Keys

Lancet Editorial

The Robert D. Campbell Foundation

In an attempt to give some tangible expression of appreciation to Dr. Robert D. Campbell for his outstanding achievements in the field of medicine and his wide range of community activities, the First National Bank of Grand Forks, North Dakota, established the Robert D. Campbell Foundation with an initial donation of $5,000.

In addition to this sum, Dr. and Mrs. Campbell gave to the bank as trustee more than $160,000 to be transferred to the Foundation upon their death. Only income from the assets of the Foundation will be used to carry out the purposes of the Foundation. A board of trustees have been named to carry out the purposes of the Foundation. Each member of the board will serve for life and will nominate a person to succeed him, except that no successor will be named for Dr. Campbell.

Directors of the First National Bank adopted a resolution lauding Dr. Campbell's service to the community, which read "The general purpose of the Foundation shall be to advance and promote the best interests of the University of North Dakota, its students, and faculty. It shall contribute to, assist in, initiate and carry on such activities, programs, projects and endeavors as may be deemed by its trustees to be best suited to the general purpose." Income from the Foundation's assets also may be used "to enable the university to investigate and to initiate special projects not contemplated by legislative appropriation, and generally to assist the university in the advancement of education, scholarship, and morality among the people of the entire area."

Contributions from any source will be accepted by the Foundation to be used for any of its purposes. Donors may specify special conditions or place limitations upon the manner in which they wish their gifts to be held or administered.

Dr. Campbell, a graduate of the University of Manitoba Faculty of Medicine in Winnipeg, established practice in Grand Forks in 1894 after serving his internship in the Northern Pacific Hospital at Brainerd, Minnesota. In 1913, he helped organize the American College of Surgeons in Chicago, and he is the only Grand Forks charter member of the organization. He is a past president of the North Dakota State Medical Association, a member of the American Medical Association, and was chief of staff of St. Michael's Hospital in Grand Forks for twenty-eight years. He was resident physician and surgeon for the Northern Pacific and Great Northern railroads from the time he established his practice in Grand Forks until he retired. In 1930, he was made president of the Great Northern Medical Association.

Dr. Campbell interrupted his practice in 1907 and 1908 to pursue postgraduate study in Vienna and again in 1917 to enlist in the Army Medical Corps in World War I. Commissioned a captain, he was discharged a major in 1919.

Dr. Starcher, president of the University of North Dakota, has long stressed the need for more scholarships to attract outstanding students from North Dakota, many of whom go to colleges outside the state where they receive greater assistance than the university has been able to offer. Dr. Starcher said that the establishment of the Foundation and Dr. Campbell's contribution is "one of the greatest things that has happened to the university." He declared that it would have a "tremendous effect on morale of faculty members as well as present and prospective students at the university."

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BOOK REVIEWS

Arrest of Bleeding, by Jacques Roskam, M.D., 1954. Springfield, Illinois: Charles C Thomas. 71 pages. $2.75.

This monograph is primarily a documentation of the author's observations of pharmacologic influences on the bleeding time of the rabbit. His brief clinical discussion of bleeding problems is rather superficial and, in some respects, in disagreement with generally accepted concepts.

TALBERT COOPER, M.D.

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Factors Affecting the Cost of Hospital Care, edited by JOHN H. HAYES, 1954. New York City: The Blakiston Co. Volume 1. $4.00.

The American hospital is confronted with serious problems of administration and financing as the result of unprecedented expansion and growth of hospital services and the rapidly increasing costs of hospital care.

In order to meet this challenge realistically and efficiently, the American Hospital Association at a cost of half a million dollars sponsored a nongovernmental commission composed of 34 leading experts to study the Factors Affecting the Cost of Hospital Care.

This volume is a 300-page factual and statistical report devoted chiefly to the 3 most important factors responsible for hospital care.

1. How much of the increased cost of hospitalization is due to expended services?

2. How much is due to higher costs of labor and materials?

3. By what means may costs of care to the public be held to a minimum without impairing the quality of services?

Through well organized research on a national level, the commission offered 19 recommendations with virtual unanimity. Because of lack of space, the reviewer can offer only a composite summary.

The commission was an emphatic ally in favor of prepayment coverage with benefits essential for adequate care.

The support of private philanthropy for construction of hospitals and the provision of necessary facilities and services was strongly urged, rather than from tax sources.

Stress was placed on the need of community planning by careful study of the needs of the local community to avoid overbuilding in some places and the inequitable distribution of hospitals in other areas.

A plea was made for cooperation between physicians and hospitals, especially in small centers, to provide diagnostic and therapeutic facilities for ambulatory services; these would include outpatient services on prepayment plans. Such projects would reduce to a considerable extent the present demand for unnecessary inpatient services.

Finally, the commission wisely suggested that in view of the many complaints and misunderstandings, a program of community education on the costs and values of hospital care be launched.

It is to be hoped that these important contributions will be digested and assimilated by the medical profession, the hospital administrators, and the general public in order that they may better understand the factors that affect the cost of hospital care.

MAX SEHAM, M.D.

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

Difficulties in Diagnosis of Atypical Duodenal Ulcer

Report of Two Cases

ROBERT C. PAINTER, M.D.
Grand Forks, North Dakota

PHYSICIANS are continually encountering patients who present a multitude of abdominal complaints, many of which may be suggestive of the peptic ulcer syndrome and many others which are obviously more characteristic of the functional types of bowel distress. Few of us need to be reminded that our original clinical impression may or may not be supported by confirmatory investigative means,[1] the roentgen examination being the most informative of these. This fact tends to keep us aware of the possibility of organic disease in any abdominal disorder and, of course, enhances the free use of the gastrointestinal roentgen examination, thus bringing quick and more accurate diagnosis in most cases with frank abdominal complaints.

We are, of course, indebted to Moynihan[2] for his excellent description of the pain in peptic ulcer. Any patient complaining of epigastric distress or pain which begins typically at a more or less fixed time after meals, is relieved by vomiting, food and alkali, and occurs daily for weeks or months at a time and then is separated by weeks, months, or years of complete freedom, presents a problem highly suspicious of peptic ulcerative disease. Such a patient will undoubtedly be investigated further by any conscientious physician in order to confirm his clinical diagnosis.

In this presentation, we do not wish to stress diagnosis in this type of case nor even in those patients who have normal upper gastrointestinal roentgenograms in spite of histories as highly suggestive as the preceding. Instead, we wish to point out the wide variations possible in symptomatology in the presence of an active duodenal ulcer. Most difficult, probably, is the problem of no gastrointestinal symptoms until some major complication ensues. On the other hand, we must be constantly aware of the frequency with which the clinical diagnosis of peptic ulcer is unrecognized because of atypical signs and symptoms which appear to point away from the gastrointestinal tract rather than to it. The following case history is illustrative of this problem.

Case 1. V.M., a 22-year-old single school teacher was first seen on January 24, 1955, complaining of back pain off and on over the previous five months. At the onset, in August 1954, she consulted a physician who found a normal dorsal spine roentgenogram but stated the blood "showed arthritis." No definite therapy was instituted, and in subsequent days she sought chiropractic treatment which resulted in further aggravation of her distress. Finally, in September, while she was still having per-

ROBERT C. PAINTER, *a 1941 graduate of the University of Chicago School of Medicine, is instructor in medicine at the University of North Dakota School of Medicine and a staff member of Deaconess and St. Michael's hospitals, Grand Forks.*

Presented at the regional meeting of the American College of Physicians, Jamestown, North Dakota, September 10, 1955.

sistent dorsal back pain, an episode of nausea and vomiting caused her to call a physician to her home. At this time, examination was essentially negative and she was advised to follow a bland diet and given an antispasmodic. She was also advised to have a more complete examination as soon as possible. However, all of her symptoms appeared to subside after this episode and nothing further was done. During the fall of 1954, the patient was teaching physical education in another town and evidently had very little trouble except she felt she "had to take it easy." About December 17, 1954, however, her dorsal back pain recurred and was persistently present daily thereafter. The distress was a dull but moderately severe pain in the lower dorsal area with radiation bilaterally around the chest into the epigastrium on occasion. The pain occurred at night as well as during the day, usually lasting one to three hours at a time, but did not appear to follow any set pattern. She denied any definite relation to exertion, though stooping and lifting sometimes seemed to aggravate the pain. She did not feel that eating helped the distress, though perhaps generally she felt better when the stomach was full rather than empty. Occasionally, when the pain was most severe, associated nausea and very infrequently vomiting occurred which did not give any definite relief. She consulted a local physician who repeated the back roentgenograms and again found them normal. After physiotherapy, analgesics, and restricted activity failed to provide relief, the patient was referred for orthopedic evaluation as a possible "disk." The orthopedist again interpreted the spine roentgenograms as normal, found a sedimentation rate determination to be 17 mm. in one hour, and suggested Novocain injection in an attempt to relieve what he felt could well be radicular pain.

This same day the patient presented herself at the Grand Forks Clinic and related the preceding story. A careful history failed to reveal further symptoms, except that nausea had occurred more frequently in recent weeks, appeared to be worse when the back pain was present, and food and vomiting had no effect whatsoever on either the back pain or the nausea. Past history was not noteworthy except for the fact that the patient had been an orphan reared by a maternal aunt who had four children of her own. A high school and college educaiton had been obtained with much sacrifice and effort. Through all these years, the patient had been quite independent in action and a source of concern to her aunt, whose efforts to help her were frequently refused. When first seen, examination of the back was essentially negative and roentgenograms of the dorsal spine, which she had brought with her, were again interpreted as normal. The patient was quite defensive and almost hostile in her attitude. At this time, she was advised to have a complete physical examination including an upper gastrointestinal roentgenogram series.

On January 29, a physical examination revealed a 22-year-old well-developed, well-nourished female whose weight was 152¾ lb. and height 5 ft. 5 in. The temperature was 98° F. The pulse was 72 and blood pressure 120/80. On percussion, minimum tenderness was present over the lower dorsal spine. The remainder of the physical examination, including a careful neurologic examination, was within normal limits. Routine examination of the urine was negative for albumin and sugar, and microscopic examination of the sediment was negative. Examination of the blood showed a hemoglobin of 14.0 gm., a white cell count of 7,550, and a normal differential. The sedimentation rate was 20 mm. in one hour. A serologic test for syphilis was negative.

Roentgen examination of the upper gastrointestinal tract revealed a normal stomach but definite rugosity of the duodenal bulb with a large ulcer crater 1 cm. in diameter in the midportion of the bulb. Because of the severity and persistence of the patient's distress, it was felt wisest to hospitalize her for treatment. Accordingly, she was admitted to St. Michael's Hospital on February 1, 1955.

After admission, she was placed on a strict program consisting of 3 strict ulcer meals per day, antacids and milk every half hour alternately, mild sedation, and antispasmodics. Almost immediately she obtained a modicum of relief from symptoms. However, pain recurred about once each day, usually between 4:00 to 5:00 P.M., but occasionally during the early night. Though the pain lasted a much shorter period of time (about one hour) and was less severe, the fact that it recurred was most distressing and frustrating to the patient. Neuropsychiatric consultation at this time failed to reveal any positive neurologic signs. However, her existing psychoneurotic personality could not be questioned. The need for this patient to be accepted and to identify herself with someone or some group was pointed out. Her strong religious tendencies and excellent intelligence were felt to be her most important assets. After daily psychotherapy and persistence of the ulcer program, she became asymptomatic and was dismissed on February 9. She has remained so since that time, being on a liberal ulcer program when last seen on June 15, 1955.

Rivers[3,4] has placed peptic ulcer symptoms into two categories or syndromes. The *visceral ulcer syndrome* includes those typical characteristics described so aptly by Moynihan and noted previously in this paper. During this stage the ulcer has involved only visceral tissue, and pain sensations are presumably carried over sensory afferent fibers which accompany splanchnic nerves passing through the sympathetic trunk along the rami communicans to the posterior roots, eventually reaching the spinal cord in the posterior horn.

A second group of symptoms is referred to as the *somatic syndrome* and arises as a result of involvement of surrounding somatic structures by the penetrating or perforating inflammatory process. In this situation some of the basic characteristics of the visceral ulcer syndrome are maintained, but as neighboring organs are invaded and as normal physiologic processes become increasingly disturbed, symptoms might well be assumed to arise which serve to substitute for or complicate the original syndrome. Pain may now be present which is dependent for its position and reference upon the particular anatomic structure involved; for example, lesser omental tissue, anterior abdominal wall, diaphragm, or pancreas. This additional pain is frequently more constant, perhaps more easily localized, but often may be little or not at all affected by the usual methods for relief of the visceral ulcer syndrome.

Applying this line of reasoning to the preced-

ing case, there is no question that the visceral ulcer syndrome had been negligible or that the complication caused by penetration of the ulcer, presumably posteriorly, had produced a somatic syndrome of such an extent that the original symptoms had been entirely forgotten or minimized by the patient. The psychiatric picture, reluctance to respond promptly to the usual ulcer program, and the location of the referred pain also suggests posterior penetration, possibly pancreatic.

The next case illustrates an example in which the diagnosis was made only after a major complication had called attention to the possibility of a duodenal ulcer.

Case 2. E.K., a 29-year-old electrician was admitted to the Deaconess Hospital, Grand Forks, North Dakota, on May 20, 1952, because of weakness, diaphoresis, and pallor associated with several tarry stools over the previous three to four hours. History failed to reveal similar difficulty previously nor any definite gastrointestinal symptoms previously. One month previously he had been treated for an acute prostatitis which had been ushered in with dysuria, frequency, hematuria, and a temperature of 101° F. Urine examination at that time showed many white blood cells and a few red blood cells in the centrifuged sediment. Symptoms responded promptly to oral Chloromycetin and intramuscular penicillin, but an exacerbation of symptoms on May 9, 1952, was treated with oral penicillin and sulfa with apparent complete relief.

On admission the patient appeared somewhat pale and apprehensive. Blood pressure was 100/60 and pulse 84. The abdomen was not distended, bowel sounds were normal, and digital rectal examination revealed a black stool which was strongly positive to the guaiac test. The remainder of the physical examination was essentially negative. Routine examination of the urine was negative for sugar and albumin. Microscopic examination of the urine sediment showed a rare white blood cell. Examination of the blood showed a hemoglobin of 9.2 gm. (59 per cent), white blood count of 9,400, and a normal differential. The platelet count, bleeding time, and coagulation time were all normal. A serologic test for syphilis was negative.

The patient was placed on a conservative program, and within twenty-four hours the blood pressure had stabilized at 114/80, pulse at 72, and the patient was essentially asymptomatic. During the remainder of his hospital stay and after discharge, the patient was on a Sippy-type strict ulcer program. Roentgen examination of the upper gastrointestinal tract on May 28 was completely normal in spite of a careful search for a possible site of bleeding. When dismissed on May 29, the blood hemoglobin was 10.5 gm. (68 per cent). A colon roentgen examination on June 3 was also completely normal. However, because of the unquestionably massive gastrointestinal bleeding, in spite of the paucity of symptoms, re-examination of the upper gastrointestinal tract was advised in one month.

Accordingly, on July 3, 1952, such a roentgen examination was done and revealed an ulcer crater in the duodenal bulb. The patient had remained asymptomatic, however, and a review of his history again failed to elicit any ulcer-type symptoms. When last seen in March, 1955, the patient had had no further difficulty and continued to follow a mild ulcer program.

In retrospect, no clues were found which might have made the correct diagnosis possible prior to the episode of massive gastrointestinal bleeding. The fact that the roentgen examination done soon after the episode occurred was negative and yet one month later a definite ulcer crated could be demonstrated, in spite of his being asymptomatic on a strict ulcer program, indicates that the bleeding may have occurred from a very small superficial ulcer which had not been extensive enough to produce the visceral ulcer syndrome. Without wishing to bring up the acid stimulation versus contraction of the gut controversy[5–7] in regard to the cause of ulcer pain, the possibility championed by Pickering[8] must be considered of a sensitive ulcer crater containing rather deep nerve endings that can be stimulated by a chemical irritant. We do not know where these pain nerve endings are and, therefore, how deep the ulceration must be before pain occurs. Pain nerve endings may possibly be unevenly distributed over the stomach and duodenum, and in some situations ulcers may be painless until they perforate or bleed.

SUMMARY

Reports of 2 cases have been presented which illustrate the widely divergent symptoms that may be expected to be seen in patients with duodenal ulcer. Rivers classification of the visceral ulcer syndrome and the somatic syndrome has been briefly discussed. Apparently no definite rules of behavior can be formulated which invariably apply to the pain or syndrome caused by peptic ulcer. However, a carefully evaluated history is still the most reliable tool we have to prevent an active peptic ulcer from escaping suspicion and recognition.

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Recent Developments in the Biochemistry of Cardiac Muscle

A Review

R. W. VON KORFF, Ph.D.

Minneapolis, Minnesota

TODAY the biochemistry of cardiac muscle is being studied as intensively and with the same degree of fruitfulness as biochemical studies of other tissues such as liver and kidney. Within the past few years, heart muscle has been found to be an excellent source of many enzymes. As a consequence, the elucidation of many biochemical problems has been accomplished. Such work, in addition to its value for the pure enzymologist, has provided large blocks of information for the biochemist, the physiologist, and the medical investigator interested in an understanding of normal and pathologic conditions of the heart. The full significance of much of the contemporary work will be realized only as additional progress is made permitting a more complete understanding of the complex functioning heart.

Some of the recent developments in biochemistry made possible by the isolation and purification of solubilized enzymes from heart muscle will be reviewed. More complex and organized enzyme systems such as the mitochondrion have been investigated extensively and will also be discussed. The relationship of isolated enzymes and organized enzyme systems to the metabolism of cardiac slices will be considered.

SOLUBILIZED CARDIAC MUSCLE ENZYMES

The cell contains a number of enzyme systems. Of these, the glycolytic and the tricarboxylic acid cycles and associated enzymes have been studied most extensively. The glycolytic system, which is anaerobic, converts glucose to lactic acid. The enzymes are present in the cytoplasm and may be isolated from the supernatant fluid after high-speed centrifugation of a tissue homogenate. The glycolytic enzymes are classified as soluble.

The enzymes of the tricarboxylic acid cycle are associated with the intracellular particulate bodies termed mitochondria *(vide infra)*, and their solubilization, or release from the particles, requires drastic measures such as repeated freezing and thawing or the use of supersonics or of surface-active agents. Enzymic mechanisms in the citric acid cycle have been treated recently in a comprehensive review by Ochoa.[1] "Solubilized" is a relative term and will be used in this text referring to an enzyme which, after dissociation from particulate matter, will not sediment at a centrifugal force of 144,000 x g. in one hour.

The tricarboxylic acid cycle results in the complete oxidation of pyruvic acid (or of lactic after its conversion to pyruvic), of the acetyl moiety of acetyl coenzyme A (the end product of fatty acid degradation), or of any substance which can be converted to these compounds. The enzymes responsible for the transport of electrons to oxygen are as essential to the over-all process as the enzymes which act directly upon the substrate.

Until recently, few details concerning the mechanism of these aerobic processes were known. As methods for the solubilization, isolation, and purification of the enzymes were developed, the reactions could be studied in detail.

The following abbreviations are employed: KG, *a*-ketoglutarate; CoA, coenzyme A; DPN^+, oxidized diphosphopyridine nucleotide; DPNH, reduced DPN^+, succinyl CoA, succinyl coenzyme A; AcCoA, acetyl coenzyme A; AcAcCoA, acetoacetyl coenzyme A; GDP, guanosine diphosphate; GTP, guanosine triphosphate; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine-5-phosphate; P_i, inorganic phosphate, PP_i, inorganic pyrophosphate; TPP, thiamin pyrophosphate; $\overset{S}{\underset{S}{}}\!\!>\!\text{Lip}$ oxidized lipoic acid; $\overset{HS}{HS}\!\!>\!\text{Lip}$ reduced lipoic acid; $\overset{AcS}{HS}\!\!>\!\text{Lip}$ acetyl lipoic acid; cyto c Fe^{+2}, reduced cytochrome c; and cyto c Fe^{+3}, oxidized cytochrome c.

a-ketoglutarate oxidation. This oxidation, one of the key steps in the citric acid cycle, is now believed to proceed as follows:[2-5]

1.

$$KG + CoA + DPN^+ \xrightarrow{KG\ dehydrogenase} Succinyl\ CoA + DPNH + CO_2 + H^+$$

It is customary to refer to a complex enzyme system catalyzing the aerobic oxidation of a substrate via several steps as an oxidase. When the enzyme responsible for the primary anerobic dehydrogenation, as illustrated in equation 1, has

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

been purified and the reaction mechanism elucidated, the enzyme is usually designated as *dehydrogenase* prefixed by the substrate acted upon. Thiamin pyrophosphate and thioctic acid are apparently necessary coenzymic components of the reaction (see *Pyruvate oxidation*). Thioctic acid, or 6,8-dithiooctanoic acid, and some of its derivatives have been designated in numerous ways during the course of their discovery and identification. The terms acetate replacing factor, pyruvate oxidation factor, protogens, and lipoic acids have been used. The terms thioctic acid and *a*-lipoic acid are now used specifically in reference to 6,8-dithiooctanoic acid both in its reduced form and its oxidized, or cyclic disulfide, form. Succinate and CoA are released for further reaction in one of several ways: (a) a simple hydrolytic deacylation.[6]

2.

$$\text{Succinyl CoA} + H_2O \xrightarrow{\text{Succinyl CoA deacylase}} \text{Succinate} + \text{CoA}$$

resulting in a loss of the high-energy bond of the acyl thioester of succinyl CoA. The acyl CoA compounds, such as AcCoA, succinyl CoA, AcAcCoA, and butyryl CoA, are acyl thioesters in which the acyl group is esterified to the active sulfhydyl group of CoA. The acyl thioesters have a free energy of hydrolysis of approximately 12,000 calories per mole,[7] comparable to the high-energy phosphate bonds of acetyl phosphate[8] and ATP.[9] The reaction system represented by the sum of reactions 1 and 2 has been utilized for the rapid assay for coenzyme A[10] and was of particular value in the development of the procedure now utilized for the commercial production of purified coenzyme A.[11] (b) A substrate level phosphorylation[5, 12] represented by equations 3 and 4.

3.

$$\text{Succinyl CoA} + \text{GDP} + \text{Pi} \xrightarrow{\text{Phosphorylating enzyme}} \text{Succinate} + \text{GTP}$$

4.

$$\text{GTP} + \text{ADP} \xrightarrow{\text{GTP–ADP Transphosphorylase}} \text{GDP} + \text{ATP}$$

which results in a retention, as phosphate bond energy, of oxidative energy released in the reaction of equation 1. The over-all reaction, resulting in phosphorylation, may be represented by the sum of equations 1, 3, and 4:

5.

$$\text{KG} + \text{DPN}^+ + \text{ADP} + \text{Pi} \rightarrow \text{Succinate} + \text{DPNH} + \text{ATP} + CO_2 + H^+$$

The participation of guanosine triphosphate in these reactions has been demonstrated recently[13] and represents the discovery of a hitherto unknown coenzyme. Reactions 3 and 4 are reversible, and, therefore, phosphorylating enzyme is capable of activating succinate via ATP to form succinyl CoA. The latter participates in other reactions such as (c) porphyrin synthesis via condensation with glycine[14] and (d) as a priming agent for the activation of acetoacetate.[15, 16]

Formation and cleavage of acetoacetyl coenzyme A. A very active enzyme exists in heart muscle catalyzing reaction 6.

6.

$$\text{Succinyl CoA} + \text{AcAcO}^- \xrightarrow{\text{CoA Transferase}} \text{Succinate} + \text{AcAcCoA}$$

The enzyme responsible for this exchange has been designated as CoA transferase.[16] It is present in heart but absent from liver.[17] The further utilization of acetoacetate requires an enzyme known as the acetoacetate cleavage enzyme[15] or as the acetoacetate condensing enzyme.[16] The cleavage reaction is represented by equation 7.

7.

$$\text{AcAcCoA} + \text{CoA} \rightarrow 2\,\text{AcCoA}$$

The resulting AcCoA may be oxidized to carbon dioxide and water or utilized in synthetic reactions.

The rapid oxidizability of acetoacetate by heart muscle and most other tissue as compared to its inertness in liver has been explained[17] by the relative rates in liver and heart, for example, of (1) acetoacetyl coenzyme A formation by the CoA transferase reaction and by a direct ATP activation, and (2) acetoacetyl coenzyme A breakdown by the action of acetoacetyl CoA deacylase and by cleavage enzyme.

Pyruvate oxidation. The purification of pyruvic oxidase has not been accomplished to an extent comparable to that of KG oxidase. Sanadi and Littlefield,[18] using enzyme prepared from pigeon breast muscle, and Korkes and associates,[19] using enzyme from pig heart muscle, have shown the over-all reaction to be:

8.

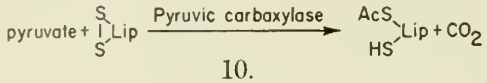
$$\text{pyruvate} + \text{DPN}^+ + \text{CoA} \rightarrow \text{AcCoA} + \text{DPNH} + CO_2 + H^+$$

This reaction is completely analogous to that of KG oxidation.

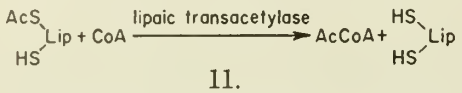
At present, the role of thiamin pyrophosphate and thioctic acid as coenzymes for the oxidation of *a*-keto acids is being studied extensively. Thioctic acid, while shown to be present in purified preparations of KG and pyruvic oxidases[3, 18] from heart muscle, has not been demonstrated as participating directly in the oxidations by animal tissue enzymes. Its role is inferred from its occurrence in these animal enzymes and from the demonstration of its essentiality for the oxidations by bacterial enzymes. Presumably, the enzymes from animal tissues contain saturating quantities as part of a tightly-bound prosthetic group. The exact role of TPP is uncertain, but it is believed to participate in the decarboxylation

reaction, while thioctic acid is known to participate in the following reactions.[20,21,22]

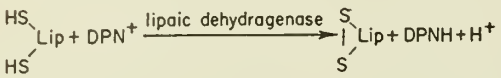
9.



10.



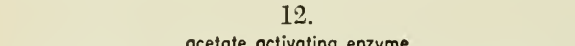
11.



The sum of equations 9, 10, and 11 yields the reaction of equation 8. The resulting AcCoA may undergo oxidation to carbon dioxide and water or be utilized in numerous synthetic reactions.

Acetate activation. The mechanism by which acetate is converted to active acetate, now known to be acetyl coenzyme A, was reported independently by 2 laboratories.[23-26] Lipmann and associates,[23] using yeast, and Green and colleagues,[24] using pig heart as source of enzyme, found the over-all reaction to be represented by equation 12.

12.



This reaction differs from many ATP reactions in that AMP and inorganic pyrophosphate are formed instead of ADP and inorganic phosphate. Activation of monocarboxylic acids, in general, appears to involve a split of pyrophosphate from ATP.[27,28]

A diagram indicating the key position of acetyl CoA in intermediary metabolism has been presented earlier.[29]

Investigation of the alkali metal ion requirement of acetate activating enzyme[30] indicated that the solubilized enzyme requires potassium, ammonium, or rubidium ion for activity and is strongly inhibited by sodium or lithium ion.

The acetate activating enzyme coupled with citrate condensing enzyme and malic dehydrogenase has been utilized for a rapid, specific spectrophotometric microassay for acetate.[31]

Citrate condensing enzyme. This enzyme, responsible for the condensation of acetyl coenzyme A and oxalacetate, was the first enzyme of the citric acid cycle to be obtained in crystalline form.[1,32] The purification was accomplished with enzyme isolated from pig heart. Fumarase, the second Krebs cycle enzyme to be obtained in a crystalline form, was also obtained from heart muscle.[33] Fumarase reversibly catalyzes the hydration reaction fumarate ⟶ malate.

DPN-cytochrome c reductase. This enzyme, catalyzing one of the pathways of reoxidation of DPNH formed in reactions such as those of equations 1 and 8, has been purified from pig heart muscle and studied by Mahler and associates.[34-36] The reductase reaction is represented by equation 13.

13.

It has been found that this enzyme is a ferroflavoprotein.[36,37] As a result of these studies, it is now believed that this enzyme, by loss of its iron, gives rise to the diaphorase of Straub. Diaphorase is a flavoprotein which catalyzes the oxidation of DPNH utilizing dyes, such as methylene blue or indophenol, as oxidants but which will not function with cytochrome c as the oxidant.

Lactic dehydrogenase. Extensive studies on lactic dehydrogenase purified from heart muscle have been made by Nielands.[38-40] This enzyme is the well-known protein catalyzing the interconversion of pyruvate and lactate. (Lactic dehydrogenase is found in the cytoplasm and therefore should not be classified under the term "solubilized" enzyme as used in this review.)

14.

Fatty acid oxidation. Space does not permit a discussion of the brilliant recent work on fatty acid oxidation, which, although largely performed with enzymes from liver, has also been accomplished in part using enzymes isolated from heart.[41-43]

Succinic dehydrogenase. Recently, success has attended attempts at solubilization of the enzyme, succinic dehydrogenase, which heretofore has resisted all efforts to dissociate it from the larger particles with which it is associated. Green and associates,[44] using desoxycholate, have purified this enzyme fifteen- to twenty-fold over the activity associated with mitochondrial suspensions. The enzyme was found to contain 4 moles of hemin and 12 to 16 atoms of nonhemin iron per mole of enzyme. The isolated enzyme contains 61 per cent lipin by weight, which undoubtedly explains the difficulty of obtaining "solubilized" aqueous preparations.

Miscellaneous. Bachhawat and associates[45] have recently reported on carbon-dioxide fixation in heart extracts by β-hydroxyisovaleryl CoA. The addition of carbon dioxide to this substance yields β-hydroxy-β-methylglutaryl CoA. The latter is capable of undergoing an enzymatic cleavage reaction to yield acetoacetate and acetyl CoA.

INTRACELLULAR PARTICULATE COMPONENTS OF CARDIAC MUSCLE

Most of the studies to be reviewed are concerned with the biochemistry of the intracellular gran-

ules, designated in American literature as mitochondria and in the English literature as sarcosomes.[46] Kitiyakara and Harman,[47] in studies with pigeon breast muscle particulates, use Opic's term "cytochondria," referring to all recognizable cytoplasmic bodies. The term mitochondria is reserved for the large granules exhibiting swelling in hypertonic solutions, while the term sarcosomes is used for the small granules described by Floegel.

General properties. The mitochondrion is responsible for the bulk of the aerobic metabolism of cells. Tissues which undergo prolonged and strenuous activity, such as heart, diaphragm, and breast muscle of birds, have high rates of oxidative metabolism and high mitochondrial density per unit of tissue wet weight.[48] The kidney, which also requires large energy supplies for its function, has a very high mitochondrial density.

The phenomenal properties of these macromolecular, multienzyme components of the cell have been described in several recent reviews by Green.[49-51] Cleland and Slater[46] have discussed the isolation, structure, and behavior of heart granules under various conditions.

Mitochondria contain all the enzymes and coenzymes necessary for the complete oxidation of any member of the citric acid cycle, of fatty acids, and of many amino acids. They are capable of carrying out many synthetic reactions such as the synthesis of fatty acids, many amino acids, the esterification of inorganic phosphate by a process known as oxidative phosphorylation, and acetylations, as well as other acylations.

The integrated and cyclical nature of the reactions catalyzed by the mitochondrion[49] prevents detailed analysis of individual steps in the reaction sequence when the intact mitochondria are investigated. It is necessary, therefore, to solubilize, isolate, and study the enzymes responsible for each reaction. When this course is followed, stoichiometric amounts of rare and valuable intermediates frequently must be employed. In many instances, this difficulty may be circumvented by coupling the reaction with one or more reactions capable of regenerating certain of the reactants. For example, in the measurement of KG oxidation, it is possible to use catalytic amounts of DPN^+ and CoA by coupling reactions 1, 2, and 15 in the presence of glutamic dehydrogenase and ammonium ion.

15.

$$KG + DPNH + NH_4^+ \xrightarrow{\text{glutamic dehydrogenase}} \text{glutamate} + DPN^+ + H_2O$$

thus regenerating DPN^+ and CoA. The net reaction is equation 16.

16.

$$2KG + NH_4^+ \longrightarrow \text{Succinate} + \text{glutamate} + CO_2 + H^+$$

The reaction sequence may be followed by manometric measurement of the carbon dioxide liberated.

With the isolation and study of the individual reactions, reconstruction of mitochondrial activities may be attempted. The attainment of this objective is no small task,[49] but much progress has been made as evidenced by reconstruction of the fatty acid oxidation and syntheses system in the laboratories of Green[41,42] and Lynen.[43]

On the other hand, the precise degree of organization of the constituent mitochondrial enzymes and the drastic measures required to dissociate many of them may prevent more than an approximate reconstruction of the total mitochondrial function.

In studying the processes involved in intact muscle, one must be concerned not only with the mitochondrial system but also with reaction of soluble cytoplasmic enzymes, other particulate structures, and their interrelationship with the myofibrils—a complex system indeed![52]

Intensive investigation of the enzymic patterns of heart muscle mitochondria is of recent origin. Classical procedures for isolation of the particles are usually employed involving homogenization, using sucrose[52] or saline[53,54] solutions followed by differential centrifugation.[55,56]

Citric acid cycle oxidations. Plaut and Plaut[54] have studied the oxidation of citric acid cycle intermediates by guinea pig heart mitochondria and observed the facile oxidation of all members of the cycle except citrate, cis-aconitate, and isocitrate. The failure of these compounds to be oxidized was attributed to the probable loss of a co-factor necessary for the prior activation of these compounds.

Studies have been conducted with the cyclophorase - mitochondrial system of rabbit heart muscle by Paul and associates,[57] with similar findings. However, citrate oxidation was noted.

In our laboratory, Krebs cycle oxidations have been studied,[58] using washed rabbit heart mitochondrial preparations. Of the substrates tested, *a*-ketoglutarate, succinate, acetate, pyruvate, and malate are readily oxidized; lactate and acetoacetate are not. Citrate was not studied.

Failure of lactate to be oxidized is apparently due to the absence of lactic dehydrogenase from the mitochondria, since addition of purified lactic dehydrogenase and DPN^+ to the medium resulted in lactic acid oxidation. Paul and associates[57] also failed to observe lactate oxidation by rabbit heart cyclophorase preparations.

In our experience, acetoacetate is inert in the presence of rabbit heart mitochondria but is rapidly oxidized by a rabbit heart homogenate or by rabbit heart slices. This may be expected in view of the finding[15] that the enzymes CoA transferase required to activate acetoacetate and the cleavage enzyme necessary for acetyl CoA formation from acetoacetate are found in the supernatant solution obtained during the preparation of mitochondria. Plaut and Plaut,[54] however, have reported acetoacetate oxidation in a similar system by washed guinea pig heart mitochondria. It is to be noted that the oxidation of fatty acids, acetate, or pyruvate by heart muscle mitochondria,[54] in contrast to liver, does not lead to an accumulation of acetoacetate. This is believed due to the failure of acetoacetate to be formed in any substantial quantity rather than to a rapid rate of oxidation of acetoacetate.

Pyruvate oxidation by washed rabbit heart mitochondria requires special comment. Fuld and Paul[59] observed that, with rabbit and pig heart homogenates and mitochondrial preparations, blocking of the Krebs cycle with malonate or by removal of C_4 acids by dialysis results in the formation of acetate from pyruvate. In the course of our experiments,[60] it was observed that the complete oxidation of pyruvate requires the presence of more dicarboxylic acid than does the complete oxidation of acetate. It was found that excess pyruvate is inhibitory to acetate oxidation and that acetate accumulates in the medium when a high ratio of pyruvate to dicarboxylic acid is maintained.

The mechanism of this inhibition is unknown, as is the mechanism of acetate formation in the system. Ochoa[61] has reported that, in cat heart, pyruvate is not oxidized at all unless a dicarboxylic acid is added to the medium. Acetate may be formed by a deacylation reaction (equation 2), or possibly at an earlier stage, such as the hydrolysis of acetyl lipoic acid, or by a reversal of the acetate activating reaction (equation 12).

The experimental data for the phosphorylation quotient of the one-step oxidation of pyruvate to acetate obtained by Bartley[62] with kidney preparations indicates the latter possibility as the more reasonable. If this be true, phosphorylation involving inorganic pyrophosphate must occur. Experiments designed to determine the mechanism of acetate formation in this system are being continued. It is questionable, however, whether the formation of acetate from pyruvate occurs in intact cellular systems, since dicarboxylic acid concentration would not be expected to become limiting.

Oxidative phosphorylation. The yield of oxidative phosphorylation, by guinea pig heart mitochondria with a number of substrates, has been investigated by Maley and Plant[63] and, for rat, cat, and pig heart, by Slater.[64] The phosphorylation quotients obtained were comparable to those obtained with mitochondria from liver and kidney. The phosphorylation quotient generally is defined as the ratio of the number of μ atoms of P_i esterified to the number of μ atoms of oxygen consumed.

The effect of ionic environment on mitochondrial respiration. We have studied the effect of alkali metal ions on respiration by heart muscle mitochondria.[58] This investigation was undertaken to determine if the potent effect of these ions on the soluble acetate activating enzyme system could be observed in the particulate system where complete oxidation of acetate to carbon dioxide and water occurs. The initial step in the total oxidation also requires activation of acetate to acetyl CoA.

Stabilizing effects of K^+ and Rb^+ were observed, but Na^+ and Li^+ appear to be inert. A number of other observations indicate that, in this organized system, the stabilizing effect of K^+ is not related to its stimulatory action on the acetate activating enzyme system. Thus, a requirement for K^+ is most evident when (1) the medium is hypertonic; (2) the mitochondria are isolated using more drastic measures for the preparation of the homogenate, such as the Waring blender; and (3) the hexokinase-glucose system is omitted from the system.

Finally, the ionic effect is not specific for acetate oxidation but is obtained with other substrates, such as malate and *a*-ketoglutarate. It appears likely that potassium functions in some manner to maintain the structural integrity of the complex mitochondrial unit and that the effect is most readily noted when a stress is placed upon the system.

Similar ionic effects in a liver mitochondrial system were reported earlier by Pressman and Lardy.[65]

The effect of calcium on the respiratory and phosphorylative activities of mitochondria has been studied by Slater and Cleland.[66] It was shown that calcium ion is a potent inhibitor of the oxidative activities of mitochondria and that the calcium chelating agent, ethylenediaminetetraacetic acid, prevents this inactivation. Heart muscle mitochondria appear to have a very high affinity for calcium, since it was discovered that, after isolation, the granules contained all of the calcium that was originally present in the muscle.

The relationship of mitochondrial structure and function. Harman and Feigelson[67] find that the shape of mitochondria from heart muscle is correlated with oxidative activity. Osmotic pressure influences both morphology and oxidative capacity of the mitochondria.

The effect of the osmolarity of the medium on heart muscle mitochondrial activity has been studied by others.[58,68] There appears to be general agreement that hypotonicity augments and hypertonicity depresses the oxidative rate.

Harman and Osborne[69] have been studying the relationship of cytochondria and myofibrils from pigeon breast muscle. As far as the author of this review is aware, similar studies have not been performed with these components from heart muscle. The breast muscle sarcosomes "are associated with a factor which accelerates mitochondrial oxidative rate. The maintenance of myofibrillar contractility and structure is closely correlated with the preservation of mitochondrial oxidative capacity and structure."[47]

Active transport of ions. Bartley and Davies[70] have reported several experiments on the formation of ionic concentration gradients by rat heart muscle mitochondria. The accumulation of ions by the mitochondria is dependent on oxidative metabolism. Most of the work was done with mitochondria prepared from kidney and liver. Stanbury and Mudge[71] and Macfarlane and Spencer[72] arrived at similar results in studies with liver mitochondrial preparations.

Discussion. Although a study of mitochondrial properties does not permit detailed analysis of individual enzymatic steps, much valuable information has been obtained. Initially, it was necessary to define the reactions which could be catalyzed by these particles. As yet, vigorous oxidative phosphorylation has not been observed in a nonmitochondrial system. Cell function is dependent upon mitochondria in-situ, although isolation permits a study free of the complicating reactions due to nuclei, microsomes, myofibrils, and cytoplasmic enzymes.

An extension of the investigations on interactions between mitochondria and myofibrils in isolated systems may prove to be highly profitable for a better understanding of intact cellular systems.

METABOLISM OF HEART MUSCLE SLICES

From the viewpoint of the enzymologist, the experimental system has now become "extremely complex." To some extent, results of studies with heart muscle slices[73] tend to be less definitive than those obtained with simpler systems.

The extent to which slice metabolism is representative of intact tissue metabolism is uncertain in large measure, since the proportion of cells that are cut or otherwise injured and the degree of damage are usually unknown factors.

The slice contains relatively large amounts of endogenous substrates, particularly in the early stage of an experiment. This complicates studies with specific compounds, although the use of isotopes can circumvent the difficulty to a considerable degree.

Experiments with slices are of value for several reasons.

1. Certain metabolic effects fail to appear at lower levels of organization, for example, the effect of cardiac glycosides.[74, 75]

2. The complexity of the material represents a more normal balance of interacting systems, such as the reactions of an anaerobic and aerobic metabolism. Isolated subcellular systems and simple reactions are not subject to many of the control mechanisms existing in the cell.

3. The slice represents an organized cellular system, yet the course of metabolism is free of influences by mechanical activity of the preparation.

4. Study of the slice provides opportunity to obtain confirmatory data bearing out the results observed with simpler systems.

The respiratory rate of heart slices, using various substrates and conditions, has been measured by a number of investigators.[74-83] Glucose has only a small effect on the respiratory rate, although the rate is maintained for a longer period than in the control flasks.[74,77] Lactate accumulates aerobically.[74] Lactate, pyruvate, and other Krebs cycle intermediates result in marked increases in the oxygen uptake by the slice.[74, 77, 78, 82, 83]

At high lactate or pyruvate concentration, a large fraction of the substrate disappears nonoxidatively, although glycogen levels are not increased.[78] In view of the pronounced effect of Krebs cycle intermediates on the rate of oxygen consumption by slices, it seems surprising that glucose, which gives rise to pyruvate and lactate, has relatively little effect on the QO_2.

Wollenberger[74] reports that the cardiac glycoside, ouabain, at a concentration of 5×10^{-7} M, decreases the production of lactate from glucose and increases the amount of glucose oxidized in spite of a decreased glucose utilization. Wollenberger believes his studies indicate that the drug involves a shift in the lactic dehydrogenase reaction (equation 14) in the direction of pyruvate. He deduces that this may occur as a result of an increased rate of DPNH reoxidation. It would appear that the "steady state" concentration of DPNH is of more importance here than its rate of oxidation. Since Wollenberger found that glucose utilization and lactate production decrease while respiration increases, his observa-

tions would appear to be explicable by a decreased rate of glycolysis with a concomitant decrease in production of DPNH by the triose phosphate dehydrogenase reaction (equation 17).

17.

$$\text{3-phosphoglyceroldehyde} + \text{DPN}^{+} + \text{Pi} \longrightarrow \text{1,3-diphosphoglyceric ocid} + \text{DPNH} + \text{H}^{+}$$

As a result, the oxygen consumption could be increased in spite of a decrease in the total amount of pyruvate produced from glucose by glycolysis.

Brin and associates[79] found that D(−)-lactate and L(+)-lactate disappear at about the same rate from the medium although the former is oxidized more slowly. In experiments utilizing labeled substrates, Miller and Olson[78] concluded that lactate utilization by the heart is limited by its rate of conversion to pyruvate.

The effect of ionic environment on heart muscle slice metabolism has been touched upon briefly. Pearson and associates[82] reported that the omission of Ca^{++} or of Ca^{++}, Mg^{++}, and K^{+} gave no change in the QO_2 of rat heart slices. On the other hand, Bernheim and Bernheim[81] found that the removal of K^{+}, Ca^{++}, or Mg^{++} had little effect, while the omission of all 3 ions from the media resulted in a marked depression of respiration. In studies with rabbit heart slices, we have observed consistently higher rates of respiration in a Ca^{++}-free medium. Dickens and Greville[84] have reported that the respiration of rat brain slices is also decreased by Ca^{++}.

Stadie and associates[85] found that glycogen synthesis in heart muscle slices proceeded most satisfactorily at very low cation concentrations and in the absence of K^{+}. A similar enhancement of glycogen synthesis by liver slices did not occur at low ionic strength.

Preliminary experiments in these laboratories have shown a consistent and prolonged respiratory response by heart muscle slices on addition of ATP to the medium with acetate as the substrate. This effect appears when other substrates are used, although, as yet, an insufficient number of experiments have been made with these other compounds. This observation is of interest since it is not general practice to include ATP in the medium used for slice respiration studies, in contrast to an almost universal use in the study of mitochondrial respiration. Perry[86] has reported that isolated rabbit heart muscle myofibrils contain about 3 μ moles of acid-labile P per gram.

Lorber[87] and Cook[88] have studied the metabolism of C^{14}-labeled butyrate by rabbit ventricle slices. The isolated lactate, pyruvate, fumarate, acetoacetate, and β-hydroxybutyrate were labeled as to be expected from the reaction sequences for fatty acid oxidation and the Krebs cycle as elucidated with isolated enzyme preparations.

CONCLUSIONS

It seems justifiable to conclude that too few of the investigations performed with heart slices have been made with due consideration of interacting systems: glycolytic, mitochondrial, microsomal, nuclear, and myofibrillar. This state of affairs stems, in part, from an inadequate knowledge of each of these cell components. Rapid progress is being made in the study of enzymic mechanisms using solubilized and purified enzymes. Knowledge of mitochondrial behavior is increasing but at a much slower rate. Barely a beginning has been made in the study of interactions of enzyme systems in the various possible recombinations.

When one considers that the living cell contains many enzyme systems precisely arranged and complicated by the presence of cell and nuclear membranes, it is understandable that our knowledge of intact tissues is woefully inadequate. An evaluation of the metabolism of an intact organ or of an entire animal appears to be a prodigious task. However, the situation is not at all hopeless. The fruits of applied research thrive on the trees of fundamental research. Twenty years ago, the processes of glycolysis were a vague mystery. A mere fifteen years ago, the citric acid cycle was unknown. Assuredly, biochemistry and medicine face a promising future.

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CITY HEALTH DEPARTMENT, 1895

To appreciate the present, it is sometimes desirable to look back at the past. This picture well illustrates the growth of the Division of Public Health of Minneapolis from the relatively small staff on September 26, 1895. The members in the photograph include Dr. N. H. Avery, commissioner of health (standing); Drs. C. E. Dutton (seated in front) and W. H. Hanscom (seated in rear), medical inspectors. The other member is not identified. Dr. Dutton was a member of the University of Minnesota Medical School's first graduating class. He and Mrs. Dutton were living at 1222 West 31st Street, Minneapolis, at the time of his death on November 5. Dr. Dutton was commissioner of health of Minneapolis in 1913 and 1914. His comments concerning the early medical history of Hennepin County were always of interest.

C. A. McKinlay, M.D.

Diagnosis and Treatment of Anorectal Diseases

GASPAR ANGELO, M.D.
Cambridge, Massachusetts

THIS PRESENTATION will deal with a review of some of the salient features in the diagnosis and treatment of the more common diseases of the anus and rectum. No area in the body receives so little attention, and no pathology causes the patient more discomfort.

A short review of the applied anatomy is essential to better understand the symptomatology of the region. The anal canal begins above with the continuation of the rectum as it passes through the pelvic diaphragm. This canal is only 1½ in. in length in the relaxed state and less than 1 in. in length when the sphincter is in normal contraction. In the embryologic development at about the ninth week, an anal dimple forms in the ectoderm; and the hindgut, made up of entoderm, extends caudad. In the region in which these join, known as the mucocutaneous junction or the pectinate line, one of the most important clinical areas in proctology is formed. This is where a separation takes place of the blood supply, the epithelium, the nerve supply, the musculature, and the lymphatic drainage.

The internal hemorrhoids above the pectinate line are drained by the superior hemorrhoidal veins which in turn join the splenic vein to the portal system and thus to the liver. The external hemorrhoids below the junction are drained by the inferior and middle hemorrhoidal veins which in turn join the pudendal vein to the inferior vena cava and then to the right side of the heart.

The epithelium below consists of skin — squamous epithelium — and above of rectal mucous membrane — columnar epithelium.

The nerve supply above the pectinate line is made of sympathetic and parasympathetic fibers. These nerves carry only visceral sensation. Only overdistention and contraction of the viscus causes pain. Below the mucocutaneous line, the nerve supply is derived from the central nervous system carrying impulses of touch, pain, and temperature.

The anal canal is surrounded by musculature. Above the pectinate line is involuntary (smooth) muscle and below is voluntary (striated) muscle. The line of demarcation is not sharp as these muscles overlap somewhat.

The lymphatic drainage below is to the groin and above, upward to the pelvic nodes.

Papillae are tooth-like projections formed at the mucocutaneous area. The crypts of Morgagni, 8 to 12 in number, are sulci behind valves in the same area and are deeper on the posterior aspect of the anal canal and more prone to trauma and infection. At the base of the crypts, there are duct-like structures which further communicate with small glandular tissue. These are known as anal ducts and preformed glands and are important in the spread of infection about the area. From the foregoing, it is noted that the anal canal, the papillae, and the crypts are richly supplied with sensory nerves, which explains the severe pain in pathologic conditions that occurs in this region.

The rectum begins opposite the third sacral vertebra as a continuation of the pelvic colon. It is 6 in. long and extends down along the sacrococcygeal curve. The ampulla is the enlarged portion below the middle Houston valve. There are usually 3 Houston valves consisting of crescentic folds of the whole thickness of the rectal wall. The middle valve, on the right side, is constant and is at the level of the peritoneal reflexion. The upper and lower valves, on the left side, are variable and may be absent. The columns of Morgagni are permanent, parallel folds of mucous membrane extending from the pectinate line upward. These are the columns in which the internal hemorrhoids and lymphatic channels of the area are located.

Correct diagnosis can be made in a majority of cases by paying attention to the following

GASPAR ANGELO, *a 1929 graduate of Tufts University School of Medicine, Boston, is assistant in proctologic surgery at the university and a surgeon at Mt. Auburn Hospital, Cambridge.*

Read at the Eastern Division Regional Meeting, United States Section of the International College of Surgeons in Chatham, Massachusetts, July 4, 1955.

points: a careful history, a complete proctologic examination, the necessity for re-examination in some cases, and special care in diagnosis of double conditions.[1] A detailed history not only gives a clue to the site of the pathology but may actually act as a guide to the diagnosis. Proctologic signs and symptoms usually include bleeding, pain, protrusion, swelling, discharge, itching, change in bowel habit, and loss of weight. A complete proctologic examination consists of a careful inspection of the perianal area using a good light, palpation of the area, a careful digital examination, anoscopy, sigmoidoscopy, and a barium enema. No elaborate equipment is necessary for an accurate diagnosis. At times, the diagnosis is not apparent after a systematic study. If the patient's symptoms persist, the entire examination should be repeated. The possibility of double diagnoses must not be neglected. A patient with large, protruding bleeding hemorrhoids may have a coexisting carcinoma higher up.

HEMORRHOIDS

Hemorrhoids may be described as localized varicosities of one or more radicals of the hemorrhoidal plexus of veins. Of the patients seen in our private proctologic practice in the past five years, 43 per cent had hemorrhoids as the primary diagnosis. Hemorrhoids are classified as external, internal, and combined external and internal. External hemorrhoids are covered with skin and internal hemorrhoids with mucous membrane, a simple fact that many lose track of in the treatment. The so-called external thrombotic hemorrhoid is seldom a hemorrhoid. It is nothing more than a clot of blood under the skin and should be called a perianal hematoma as Gorsch so aptly suggests.[2]

Bleeding is usually the first presenting symptom of internal hemorrhoids. The blood is bright red and, at first, occurs only with defecation. As the hemorrhoid becomes larger and starts to protrude, bleeding occurs at any time, requiring a protective pad. Hemorrhoids are the most common cause of rectal bleeding. The primary source of rectal bleeding caused by hemorrhoids may be missed if the patient is not placed in the lateral position and examined with an anoscope before sigmoidoscopy is carried out in the inverted position, as the hemorrhoids will empty out. Too often patients are submitted to repeated, complicated, and expensive examinations and even to an exploratory laparotomy, uselessly, when a properly performed anoscopy would have revealed the source of bleeding.

The patient notes a protrusion after a bowel movement which at first slips back spontaneously. However, as the condition progresses, manual replacement is necessary. A mucoid discharge is noted also, which, in turn, causes an irritation of the perianal skin with excoriation. Pain is not a common symptom with hemorrhoids. It occurs with an acute prolapse with the accompanying external thrombosis, edema, and congestion. Severe secondary anemia is common with hemorrhoids.

The treatment may be palliative, by injection, or by radical surgical repair. Palliative therapy is applicable for the minor degree of hemorrhoids, especially when associated with edema and infection. Bed rest is prescribed, and hot wet packs are applied until the condition subsides. Injection treatment of hemorrhoids is a valuable, painless procedure if properly performed. Only uncomplicated internal hemorrhoids are amenable to this type of therapy. Prolapsing external and internal hemorrhoids with ulceration, infection, and fibrosis respond best to hemorrhoidectomy. Many solutions are advocated. We favor a 5 per cent phenol in oil or a 5 per cent solution of quinine and urea hydrochloride. Cases have been reported of fatal generalized anaphylactic reactions during a course of treatment in which the patient became sensitized to the solution used.[3] The internal hemorrhoid consisting of a soft, spongy, easily bleeding swelling is converted by the sclerosing solution to a hard, contracted, fibrotic, nonbleeding area.

Great progress has been made in the surgical treatment of hemorrhoids. It is important to recognize the anatomic variations of the anus and to tailor the procedure to fit them. Postponing a hemorrhoidectomy in patients with gangrenous, ulcerated, septic prolapse has greatly reduced the postoperative incidence of inflammation, delayed healing, and metastatic infection. For the past eleven years, our routine has been to administer 3 gm. of Sulfathalidine on the day of admission to patients undergoing anorectal surgery.[4] This is continued postoperatively in 3 divided daily doses until the patient is discharged from the hospital. In addition, an ampule of 5 mg. of vitamin K is administered intramuscularly to overcome the elevation of the prothrombin, bleeding, and clotting times that Sulfathalidine may produce. The type of operation performed depends largely upon the experience of the surgeon. We find the dissection-ligature method very successful and well suited to the anatomic variations. It is important not to include muscle in the suture and to place all sutures above the sensitive pectinate line. Too

much tissue must not be included in the ligature or delayed postoperative hemorrhage may result. Oxycel is placed into each wound, and a pressure bandage is applied that is held in place by a "T" binder. No packs are employed. Prolonged anesthetics are not used. Caudal anesthesia is the anesthetic of choice. On the first postoperative day hot sitz baths are started, 1 gm. of Sulfathalidine is given three times a day, a house diet is prescribed, and normal bowel movements are encouraged. On this routine, 82 per cent of our patients have normal, spontaneous bowel movements during the first three days without the aid of laxatives, mineral oil, or enemas. On the third day, if defecation has not occurred, the patient receives an oil retention enema followed one hour later by a saline enema. On the third or fourth day after his discharge, he reports to the office for wound care until the healing is complete and the function normal.

ANAL INFECTIONS

Anal infections involve a definite sequence of inflammatory events. Nesselrod[5] divides the process into three stages. In the first stage, infectious material is caught in one of the several anal crypts and directed into the anal ducts and glands. The second stage is that of invasion of the perianal and, at times, the perirectal tissues. With further involvement, the various manifestations of anorectal inflammatory diseases develop, such as cryptitis, papillitis, pectenosis, anal fissure, anal abscess, and anal fistula.

CRYPTITIS AND PAPILLITIS

Cryptitis is an inflammation in the crypts of Morgagni. A primary diagnosis of cryptitis and/or papillitis was made in 16 per cent of our patients. Papillitis is an inflammatory process in a papilla and is associated with edema and fibrotic hypertrophy. Papillitis is usually a sequel of cryptitis. Pain and anal discomfort are perhaps the most common symptoms and are described as a dull ache becoming worse after defecation. A patient recently described a protruding hypertrophied papilla as "a piece of string with a tassel on the end of it." Many times, a constant mucoid discharge is noted. Reflex phenomena are also manifested as dysuria and retention of urine, pain in the legs, and many times flatulence with considerable muscle spasm. Examination reveals deep inflamed crypts with finger-like projections of varying sizes.

The treatment may be palliative or surgical. A mild cryptitis and papillitis respond to hot sitz baths, application of witch hazel compresses, and a nonirritating diet. It has been our experience that most patients with cryptitis and papillitis who require surgery have other pathology in addition, such as hemorrhoids, a fissure, or a pectenosis that necessitates more definitive surgery. However, a moderately enlarged papilla or an isolated infected crypt may be excised in the office with local anesthesia.

FISSURE IN ANO

An anal fissure is a radial tear or crack in the anal skin, usually located in the posterior commissure. It is one of the common and important lesions about the anus and is usually single. Only 8 per cent are located in the anterior commissure, and then usually in women who have had children. Failure to understand the pathogenesis of a fissure in ano accounts for the many failures in treatment. A fissure found in a region other than the classical posterior or anterior areas should be cause to suspect tuberculosis, chancroid, chancre, or malignancy. Usually an edematous, painful skin tag appears on the distal portion of the ulcer known as a sentinel pile.

The most prominent symptom of a fissure in ano is pain. This lesion has a characteristic pattern. The pain begins with a bowel movement, decreases with the relaxation of the muscle, and then increases as the sphincter becomes spastic, thus irritating the lesion. The pain may last one to four hours depending on how acute the fissure is. Bleeding is usually noted only on the toilet tissue. The condition may be extremely disabling.

Only an early, uncomplicated fissure heals with palliative treatment. If healing does not occur with simple treatment in three or four weeks, surgical excision is required as it is for any fissure that includes the typical triad of a sentinel pile, anal ulcer, and proximal hypertrophied papilla. The ulcer must be dissected, and the wound extended to 1 in. distal to the anal verge. A posterior sphincterotomy is then performed to relieve muscle spasm and drain the deeply infected areas.

PERIANAL AND PERIRECTAL ABSCESSES

Abscesses about the anus and lower rectum almost always originate in the crypts of Morgagni and extend through the anal ducts and glands to the perianal and perirectal spaces. Accordingly, these are classified as follows: (a) perianal abscess, (b) ischioanal abscess, (c) submucous abscess, and (d) pelvirectal abscess.

Less frequently, abscesses may arise from outside the anal canal from hair follicles or sweat glands. Of the patients in our practice, 5 per

cent had a perianal or perirectal abscess as a primary diagnosis. Signs and symptoms are generally the same as those of abscesses in other parts of the body, depending on the size and location. Usually a very tender swelling is present at the anal verge associated with heat, induration, and edema. Temperature may be elevated. The swelling develops much slower than in the case of an external thrombotic hemorrhoid.

A perianal or perirectal abscess should be incised and drained as soon as the diagnosis is made. Too many complicated fistulas result when physicians administer sulfonamides or antibiotics over long periods of time while the local pathology is still intact. These agents are ineffective unless the abscess is first drained. If the abscess is not deep-seated, incision and drainage may be accomplished in the office with local anesthesia administered as close to the anus as the fluctuation allows. The patient is warned that a fistula will occur and require future excision. Recently, when the patient is hospitalized, our custom has been to locate the primary opening at the time of incision and drainage and thus avoid multiple operations and protracted convalescence periods.

FISTULA IN ANO

Fistula in ano may be described as a contracted abscess with a primary and secondary opening. This condition occurred in 5 per cent of our patients as a primary diagnosis and was found more frequently in men. A complicating adenocarcinoma in the fistula was present in 6 patients with fistulas of long duration. Classification of a fistula is based on its location, such as: (a) subcutaneous fistula, (b) submucous fistula, (c) fistula in ano, and (d) anorectal fistula.

A patient often reports 5 or 6 operations for an attempted cure of this condition. These vain attempts at cure are chiefly due to failure to find the internal opening. Peroxide injected under pressure has frequently been very helpful because it provides the visibility but not the confusing staining of methylene blue. In complicated multiple fistulas, the injection of Lipiodol and stereoscopic x-ray studies have been very helpful in determining their extent and course. At operation, the entire tract should be excised and the resultant wound saucerized to create a flat wound. Great disability and incontinence could be avoided by not allowing a pack to remain more than twenty-four to forty-eight hours. In postoperative treatment, it is important that wounds heal by granulation from the base to prevent recurrence.

ADENOMAS

An adenomatous polyp is the most common benign tumor of the intestinal tract. This lesion is definitely premalignant. It starts first as a small, soft, sessile swelling on the mucous membrane, and then enlarges and develops a pedicle. The surface is lobulated, usually red in appearance, and may become ulcerated and infected.

The villous adenoma is a soft, sessile tumor that may cover a large surface of the rectal mucosa. This tumor consists of many villous processes and grows more slowly than an adenoma. Bleeding is the most common symptom. However, a presenting symptom may be absent. Usually the polyp is discovered on routine sigmoidoscopy. A mucous discharge, lower abdominal cramps, and change in bowel habit may occur.

A survey made at the Mt. Auburn Hospital on the occurrence of adenomatous polyps in the colon and rectum in 1,018 consecutive autopsies over a period of twenty-two years showed an incidence of 7.3 per cent, as previously reported.[6] Of these, 42 per cent were multiple; 86 per cent were found in the age group of 40 to 89 years. In a parallel study of 1,076 consecutive sigmoidoscopies in my proctologic practice, the incidence of adenomas visualized by a 10 in. sigmoidoscope was 9.75 per cent.

A barium enema is of extreme importance if sigmoidoscopy reveals an adenoma. The tumor may be a sentinel polyp indicating an adenocarcinoma above. Discovery of premalignant adenomas and early malignancies of the rectum and lower sigmoid could be achieved more frequently if sigmoidoscopic examinations were performed as follows:

1. In routine physical examinations, especially in patients over 35 years of age, and particularly in men.
2. In all patients with gastrointestinal symptoms.
3. In all patients prior to a barium enema examination.
4. In all patients preceding anorectal surgery.

Rectal cancers can be diagnosed 100 per cent by digital examination and sigmoidoscopy.

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Differential Diagnosis of Dermatoses of the Hands

JOHN G. DOWNING, M.D.
Boston, Massachusetts

STUDY OF THE HANDS may reveal beauty, genius, artistry, or labor. No features are more expressive than the hands. A handshake may reveal a personality. The firm, hearty clasp discloses friendliness or reliability; the limp, moist handshake denotes timidity or nervousness; the crushing grip reveals egotism; and the perfunctory grip indicates aloofness or lack of interest.

Chiromancers or palmists often astound listeners with their analysis of a client, which usually is a result of intuition and keen observation of the possessor of the palms. Anyone who believes the lines and mounts of the palms can be interpreted should examine babies' palms. Some markings of the hands are interesting and occasionally valuable for identification purposes, for example, calluses, cicatrices, and the stigmata of occupation. Illness also leaves its mark, as is seen in the pigmentation of pellagra and the ugly joints of arthritis.

The nerve supply of the hands reveals how training can develop the remarkable sense of touch of the blind, the deaf and dumb, the surgeon, and the musician. The differences in the various abilities of medical students to palpate the abdomen are interesting to note — some have an artist's touch, others, a blacksmith's.

The double vascular and lymphatic supply of the hands is important. As a result, infection may become either superficial or deep. If only the arteriocapillary-venous pattern is affected, it remains as a septic dermatitis, becoming deep-seated if the arteriovenous anastomosis is affected. With the former, common contact dermatitis occurs with secondary infection; with the latter, acute paronychia, subcutaneous, and fascial space infections develop. The dorsa of the hands have few lymphatics. When the outer lymphatics of the hand are infected, the axillary nodes are involved. The medium group involves the epitrochlear nodes, and the thumb and index finger involve the epitrochlear and the supraclavicular nodes.

Many manifestations of systemic diseases are revealed by the hands. Excessive sweating of the palms with flushing and tremor is seen in tension and hyperthyroidism. The myxedematous patient has cold dry hands. Tremor occurs in patients with neurocirculatory asthenia and Parkinson's disease. In the latter, tremor is an early clue. Large tapering fingers in a female with a peculiar malar flush, though not diagnostic, should suggest a chest roentgenogram.

Pigmentation of the hands in Addison's disease is usually pronounced, especially at the palmar creases. A yellow staining of these creases may be the first sign of a familial hyperlipemia. There is marked yellow discoloration of the palms in carotenemia, which can be distinguished from jaundice by its absence from the sclerae. A greenish-yellow staining of the dorsa of the hands is seen in Atabrine poisoning. The hands of patients suffering from myxedema have a peculiar waxy yellow color. A ruddy cyanosis of the distal phalanges of the fingers and toes suggests arteriosclerosis in obesity, diabetes, and gout. Pigmented macules may be seen on the hands of patients with intestinal polyposis.

Palmer erythema may be familial, but often is associated with liver disease. Spider angiomas of the palms and elsewhere on the body are seen in liver diseases and occasionally in pregnancy. Patients with cirrhosis of the liver may show complete loss of color of the fingernails. Spoon nails may develop in anemic old women who also show a smooth, shiny tongue with fissuring at the corners of the mouth. A pallor of the palms may reveal an anemia before the mucous membranes or conjunctivas are affected. The white patches of vitiligo are usually first noticed on the dorsa of the hands. Depigmentation caused by the prolonged use of rubber gloves should be carefully ruled out, especially in the colored race (figure 1).

In pityriasis rubra pilaris, the fingernails and toenails rapidly become opaque, thickened, and striated and present subungual hyperkeratosis.

JOHN G. DOWNING, *a 1915 graduate of Harvard Medical School, is professor emeritus at Boston University Medical School and Tufts College Medical School, Boston.*

Fig. 1. *(left).* Vitiligo. *(Right).* Leukoderma caused by use of rubber gloves.

A pronounced yellowish hyperkeratosis appears on the palms and soles. The dorsal aspect of the fingers shows follicular papules containing a horny center. Patients with Darier's disease frequently show thickening of the skin of the palms and soles, with subungual keratoses.

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's syndrome), frequently seen in several members of the family, first presents symptoms of epistaxis or hemorrhagic tendency after trauma. The oral and nasal mucosa and the skin of the face and hands show various types of pinpoint angiomas and telangiectasia. These differ from the spider angiomas in that they rarely pulsate and are dark red, not bright red.

Cases of epidermolysis bullosa were discovered during the recent war when soldiers suffering from excessive sweating and bullous lesions of the palms and soles did not respond to antifungal therapy. The severer type includes dystrophy of the nails. As the bullae in the dystrophic type are between the epidermis and corium, healing results in severe scarring and often loss of fingers and toes.

In children, an intense pink color and tenderness of the hands and feet are due to a possible vitamin-deficiency disease, acrodynia, or mercury poisoning. The reddish-brown scaling of the dorsa of the hands in patients with glossitis and painful ulcerations at the oral commissures and on the tongue establishes the diagnosis of pellagra or pellagroid in alcoholic persons. Blisters often appear on the dorsa of the hands (figure 2).

In trichinosis, the eyelids are swollen, with ecchymosis of the conjunctivas and splinter hemorrhages under the nails. In meningococcal meningitis, characteristic petechial hemorrhages occur in the mucous membranes of the mouth and eyes and also on the palms and soles. This fact proves helpful in diagnosing the disease in Negroes, since their skin is lighter on the palms and soles.

Pinkish maculas (Janeway's nodes) occasion-

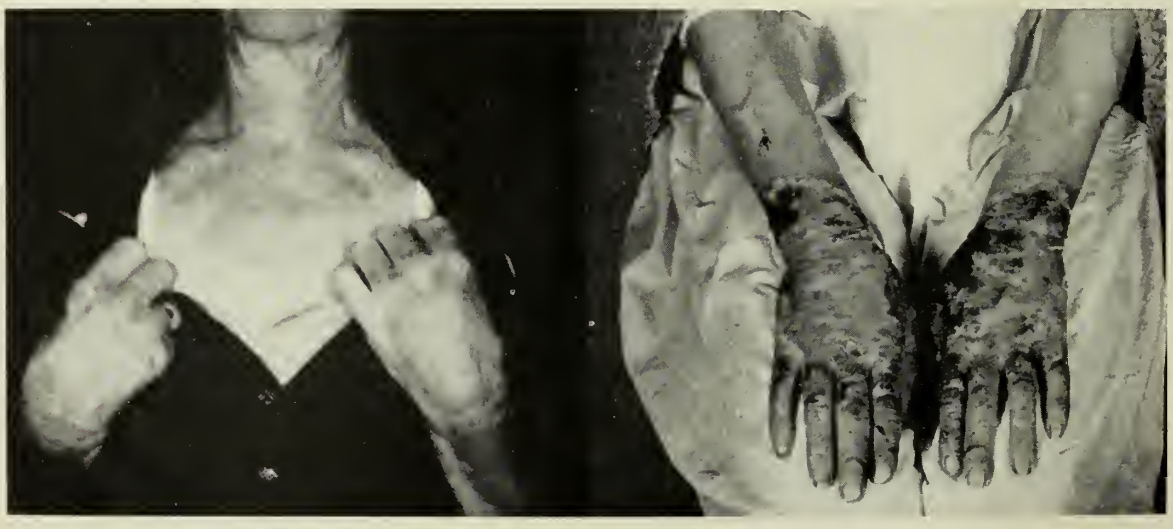


Fig. 2 (*left*). Alternating patches of brilliant erythema and pallor on hands and Casál's necklace around the neck of a pellagra patient. (*Right*). Bullous, crusted eruption after exposure to sunlight.

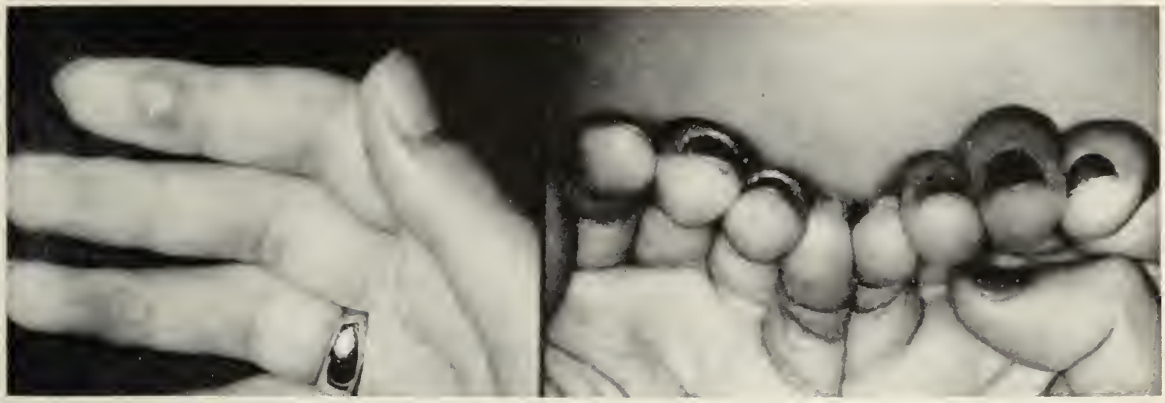


Fig. 3 (*left*). Acute lupus erythematosus disseminatus showing tender, hemorrhagic nodes and (*right*) depressed, erythematous patches on fingertips.

ally appear on the palms and fingers in bacterial endocarditis. These lesions may become hemorrhagic and later pigmented. Osler's nodes—small, red, tender swellings—may be present on the tips of the fingers and toes. Subungual splinter hemorrhages may occasionally be seen. Erythematous patches on the paronychial folds and finger pads are seen in patients with acute lupus erythematosus disseminatus (figure 3).

In berylliosis, ulcers on the exposed areas, especially on the hands, are due to local deposits of beryllium. Such ulcers are discrete and painless, unless secondarily infected, and are located over joints subject to trauma. Acrosclerosis and scleroderma often start with Raynaud's phenomena with hardening of the skin and vasospasm of the extremities. The fingers frequently present rather a dull, shiny, cream color; the joints may be painful and swollen. Raynaud's disease presents the so-called "dead" fingers, followed by swelling and congestion. The earliest permanent changes in tissues are dry, scaly depressed patches on fingertips which later become necrotic.

The deformities of arthritis range from spindle-shaped swelling of the second joints to nodules on the sides of the joints. In psoriatic arthritis, the distal joints are involved. Calcified deposits under the skin appear in gout. Huge hands are characteristic of acromegalia. Cyanosis and bulbous enlargement of the distal parts of the fingers, so-called clubbing, may be seen in congenital heart cases and chronic pulmonary disease. In children with fusiform swellings of the fingers, an avascular necrosis of the phalanges should be considered. Purpuric spots and tender, purplish-red nodules may appear on the hands of patients with periarteritis nodosa. Symmetrical desquamation of the palms may be the first cutaneous evidence that a child has had scarlet fever.

Syphilis, though rare, still occurs. The unwary physician may discover a painful paronychia on his index finger. The lesion slowly becomes red, fungoid in shape, slightly eroded, and teeming with spirochetes. The latter finding may be the only differential means of diagnosing it from the punched-out ulcer of tularemia. Secondary papular palmar syphilis may be recognized by its typical ham-colored papules with their distinctive collarette of scales (figure 4). Excessive keratotic lesions of palms are a rare complication of persistent gonorrhea.

Recurrent vesicles on one finger may be due to herpes simplex. Herpes zoster may start in its ulnar distribution with pain and tenderness of the fourth and fifth fingers, followed by vesicles which also involve the arm. A fulminating virus infection may present a severe vesiculobullous eruption of the hands, with a stomatitis and generalized skin eruption of the erythema multiforme type. The hands are frequently subjected to cat scratches and occasionally subsequent fever, adenopathy, and a macular eruption occur (figure 5).

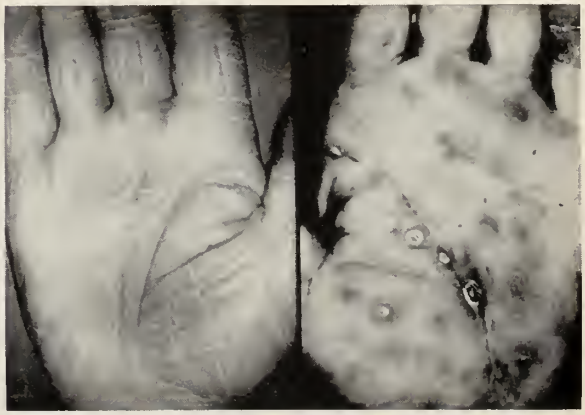


Fig. 4 (*left*). Trichophyton infection of palms. (*Right*). Palmar syphilis.

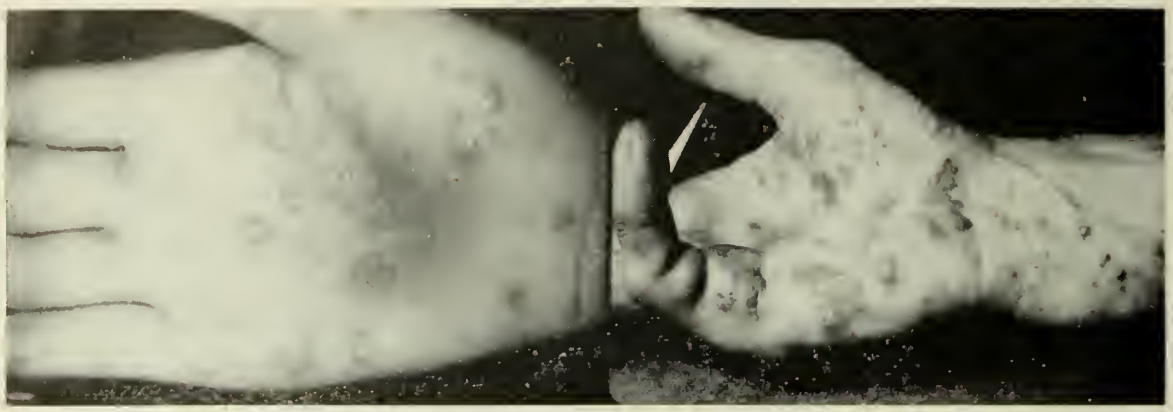


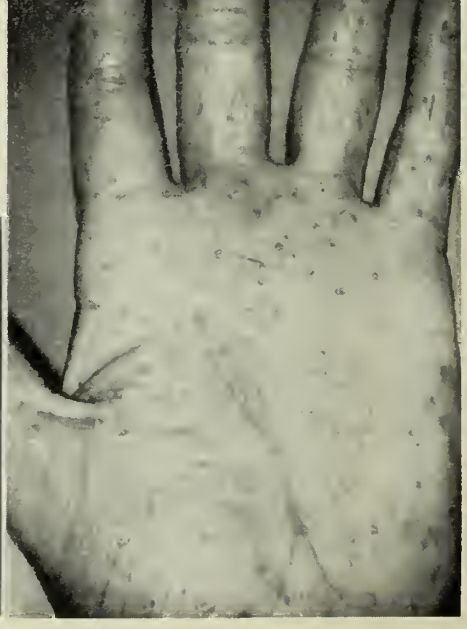
Fig. 5 (*left*). Erythema multiforme type of drug eruption from penicillin. (*Right*). Herpes zoster involving hand and arm.

The hands may present the first signs of nervous emotion with circulatory disturbances, tremor, excessive palmar sweating, and a resulting symmetrical vesicular eruption, so-called cheirophompholyx or dyshidrosis. The vesicles are deep-seated and accompanied by itching or burning (figure 6).

Drug eruptions may appear first on the palms. The keratotic papules that occur after chronic arsenic poisoning are well-known. The commonest drug eruption today consists of a symmetrical, vesicular eruption due to antibiotics. Persistent fungus eruptions of the feet may be accompanied by the so-called id reaction, usually a symmetrical eruption on the lateral aspect of the fingers and the thenar eminences of the palms. This type of id eruption can also appear as a result of an allergy from chemicals and drugs in contact with other areas of the skin. Eruptions of the hands from food allergies may occur but are difficult to prove. The so-called atopic individual may have a chronic eczema confined to the hands. The eruption is usually symmetrical, lichenified, excoriated, and intensely pruritic. These patients suffer acute recurrences from emotional episodes, dietary variations, and numerous other allergies. Their allergies seem to vary so that skin testing is of little value. However, the majority of patients show positive reactions to wool, dusts, and pollens (figure 7).

Psoriasis may be limited to the hands, manifesting various forms. As a rule, however, careful examination shows involvement of the scalp or other areas of the skin. The nails may show small pits with grooves and striations. In other cases, a yellow discoloration appears at the free border of the nail. This discoloration gradually involves the entire nail, which then loses its luster because of the formation of hyperkeratotic scales on the nail bed. The most difficult type to diag-

Fig. 6 (*below*). Acute vesicular dermatitis of the hands. (*Right*). Dyshidrosis of the palms.



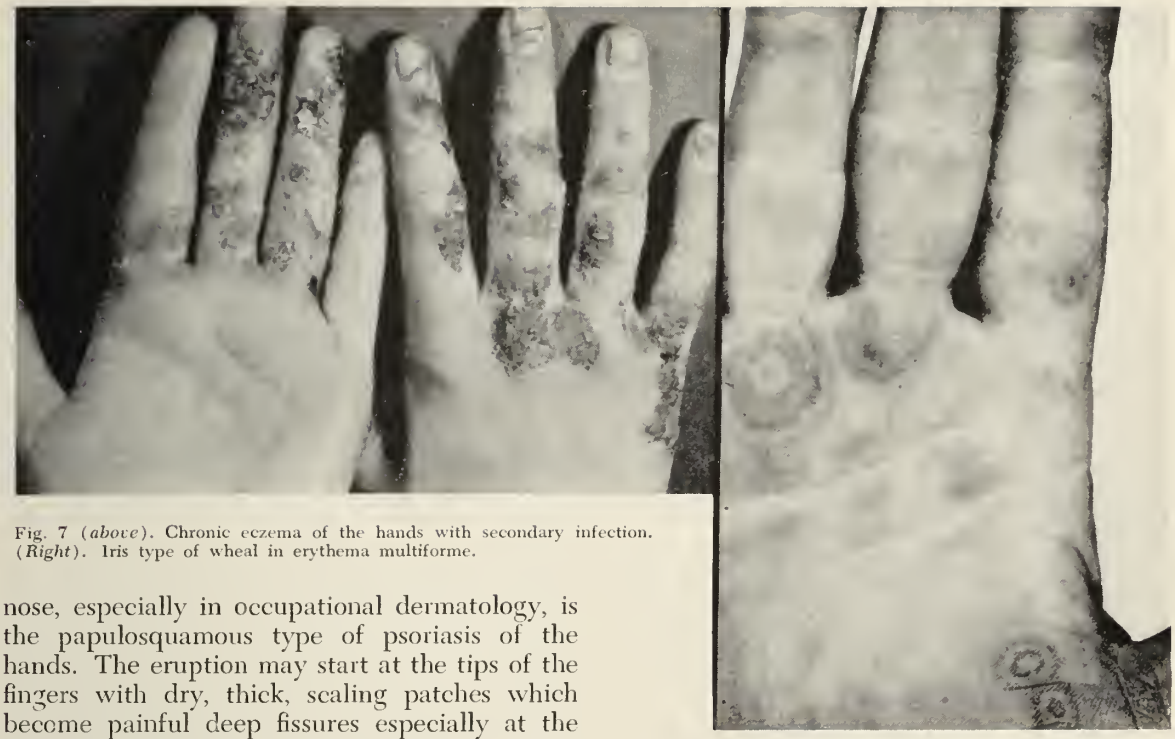


Fig. 7 (*above*). Chronic eczema of the hands with secondary infection. (*Right*). Iris type of wheal in erythema multiforme.

nose, especially in occupational dermatology, is the papulosquamous type of psoriasis of the hands. The eruption may start at the tips of the fingers with dry, thick, scaling patches which become painful deep fissures especially at the paronychial folds. The sides of the fingers and the palmar pads become covered with thick, hyperkeratotic, laminated scales. Similar scaling is usually seen on the extensor surface of the joints and on the knuckles.

A chronic, pustular, treatment-resistant type of psoriasis may also develop, usually on the thenar or hypothenar eminences. The patch is usually bright red with a silvery sheen and studded with deep-seated pustules. At various stages, these lesions are milky white and later form dark brown crusts that gradually exfoliate. Andrews described a similar eruption called pustular bacteride, which is thought to be due to focal infections. It is a recurrent symmetrical eruption consisting of crops of vesicles or pustules and accompanied by itching and swelling of the palms.

Granuloma annulare, a toxic or allergic eruption, is seen on the fingers or the dorsa of the hands and occurs most frequently in children or young adults. The initial lesion is a skin-colored, flat nodule which extends peripherally, forming an annular lesion due to involution of the center. Circular, circumscribed, elevated, red patches of vesicles on the dorsa of the hands, so-called nummular eczema, are often seen in the winter. The cause of this type of eruption is unknown, and it resists all therapy but clears spontaneously in the fall. Nutritional deficiencies should be considered in the study of the hands. Often pellagra or pellagroid eruptions are mistaken for contact dermatitides. Palmar hyperkeratoses are seen in elderly women after the menopause (figure 8).

Local agents that affect the hands are the various bacterial, fungus, and viral infections, as well as local irritants and sensitizers. In cases of acute and chronic paronychias, in addition to local treatment, pediculosis of the scalp should be ruled out even in apparently clean adults. A purplish erythema called erysipeloid, which is due to the swine bacillus, may develop in meat and fish handlers who suffer a superficial cut. It starts on the fingers and spreads to the hands but rarely becomes generalized. Occasionally bullous lesions caused by pyogenic organisms develop in these workers. Impetigo contagiosa is a common infection of the hands and a frequent complication of scabies and pediculosis. A brilliant red protrusion of granulomatous tissue may occur after trauma. The lesion, which results from a low-grade infection, bleeds readily and is called granuloma pyogenicum.

Fungus disease localized on the hands is comparatively rare and should be confirmed by direct microscopic examination or by culture. Smooth, scaly, slightly pruritic patches on the palms should suggest a Trichophyton infection of the purpureum or rubrum group. The Trichophyton fungus is easily cultured, and proof of its presence is valuable for prognosis and treatment. The nails may also be affected in Trichophyton infections, but monilial infections are

Fig. 8 (*left*). Neoplastic nodules on palms of a patient with xanthoma tuberosum. (*Right*). Keratoderma occurring after menopause.

more frequent. Monilia usually affects the paronychial fold and the interdigital skin and is usually seen after prolonged wetting of the skin. It has a characteristic brilliant red appearance with a thin macerated coating of skin. In differentiating lesions at the base of the nail, it is well to remember that this is a common area for therapy-resistant warts.

The diagnosis and treatment of disturbances of the hands constitute 80 per cent of the dermatologist's practice. Of these hand affections, 90 per cent are due to occupational or recreational pursuits. The largest group of patients are housewives affected by irritants and sensitizers encountered in their daily work. By the time the physician is consulted, these eruptions are usually of weeks' or months' duration. At this time, the initial agent is already forgotten or obscured, or the sensitization has been so gradual that it is difficult to detect. Inasmuch as removal of the cause is the most important part of the treatment, a careful history is a necessary part of the examination. When the dermatitides are complicated by a secondary infection, this must be relieved before the dermatitis is cleared. The eruption is usually eczematous and begins with erythema, edema, and vesiculation, followed by oozing and a tendency to coalesce into more or less sharply outlined, thickened, fissured plaques. Secondary infection is a frequent complication with the formation of painful pustules. The patient becomes totally disabled and very depressed. In industry, a worker who has become sensitized from the contacts of his trade may be permanently disabled and unable to resume his occupation.

TREATMENT

The majority of cutaneous eruptions of the hands are caused by medication, external irritants, or local injuries plus infection. Discovery and removal of the cause are of vast importance. Most of these eruptions start with erythema, edema, and vesiculation. Therefore, the first form of therapy should consist of wet dressings properly applied every two hours. The following wet dressings are indicated in the order of preference: aluminum acetate solution, 3 per cent; boric acid solution, 2 per cent; normal saline solution; milk; potassium permanganate, 1:7500; and tannic acid, 1 per cent. When secondary infection is present, the usual well-known antiseptics or the soluble antibiotics, preferably neomycin, tyrothricin, or bacitracin are indicated. These are the antibiotics of choice for local applications because they are rarely used systemically. Later, calamine lotion, U.S.P. XIII, may be applied followed by a zinc paste such as:

Zinc oxide	2
Cornstarch	12
Petrolatum	q. s. 30

If the skin is very tender and becomes rapidly denuded, calamine liniment N.F. may be used instead of the lotion or paste. Later, when the eruption quiets down, a paste such as the following is necessary:

Burow's solution	10
Zinc oxide	20
Petrolatum	30

Tar is needed at the end of three weeks, but should not be used if infection is present. A 3 per cent coal tar solution can be added to the above-mentioned paste, or the following tar ointment may be prescribed:

Zinc oxide	2
Crude coal tar	2
Cornstarch	5
Petrolatum	28.5

When secondary infection occurs, antibiotic ointments are necessary. A combination containing polymyxin B sulfate 5,000 units, bacitracin 500 units, neomycin 5 mg. per gram, or Terramycin 30 mg. with 10,000 units per gram of polymyxin are valuable. Alternating the above-mentioned paste with the antibiotic ointment seems to speed the patient's recovery.

Steroids are indicated in cases of extensive drug eruptions and contact dermatitis, especially if the patient is suffering great discomfort. In such cases, however, they should not be used longer than three days. Various steroids applied locally offer great relief in intensely pruritic eruptions of the hands. These substances reduce the erythema and edema present in the acute phase. For this purpose, 1 per cent hydrocortisone ointment is very satisfactory. Various useful combinations of hydrocortisone and antibiotics may be selected if secondary infection of the skin is present. One combination contains 1 per cent hydrocortisone and 5 mg. of neomycin sulfate per gram, and another contains 1 per cent hydrocortisone and 3 per cent Terramycin.

Recently a very effective steroid, 9-alpha-fluorohydrocortisone, has been introduced in a concentration of 0.05 per cent lotion and 0.10 per cent ointment. However, at the April meeting of the American Dermatological Association, Livingood and his associates[1] reported studies on a group of patients hospitalized because of dermatitis and treated with various amounts of 9-alpha-fluorohydrocortisone. They found that local use of the latter may cause significant reduction of sodium excretion in the urine and suppression of the adrenal gland, which is evidenced by reduction of 17-ketosteroids and 17-hydroxysteroid excretion in the urine. In view of this absorption, this medication should be used with caution, especially in infants, because it has demonstrated no basic advantage over hydrocortisone for topical therapy.

CONCLUSION

Routine inspection of the hands serves as an excellent diagnostic aid. While no one would believe that a disease could be diagnosed or an individual or an occupation identified by cutaneous stigmata alone, nevertheless, with the total picture, one slight additional clue may solve the problem. With the correct diagnosis established, proper therapy can be outlined. Many hand eruptions seen in private practice are irritated by improper therapy. Only a few hand eruptions are incurable. Therefore, careful selection of therapy is essential. The important problem in occupational dermatology today is rehabilitation of the worker who had an established trade and became sensitized by the contacts at his work.

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Diminishing response to skin tests with advancing age, especially after 50 or 60 years, have been noted by Louis Tuft, M.D., V. Muriel Heck, M.T. and Donald C. Gregory, Temple University, Philadelphia. Therefore, a negative result with standard dilution may indicate depressed reactivity in general rather than lack of sensitization to a specific allergen. Tests with the next stronger solution might be positive.

Cutaneous power to respond may be demonstrated with histamine. Capacity is apparently normal if a 1:100,000 dilution has slight effect and a 1:10,000 concentration slight to moderate reaction. Reactivity is probably low if results are negative with the weaker solution and doubtful or only slightly positive with the stronger solution.

Several thousand tests were done on sensitized and healthy subjects of all ages from the first to eighth decade. Both common and uncommon food allergens were employed for patients known to be susceptible. Nonallergic patients had usual intracutaneous histamine tests with 0.02 cc. of 4 concentrations ranging from 1:1,000 to 1:1,000,000.

On the whole, results were similar. However, with allergy, the number of positive reactions fell sharply after the age of 50. Response of nonallergic subjects to histamine did not decrease greatly until after 60 years of age.

Louis Tuft, V. Muriel Heck, and Donald C. Gregory: J. Allergy 26:359-366, 1955.

Heart Disease in the Infant Under 2 Years of Age

FORREST H. ADAMS, M.D.
Los Angeles, California

I HAVE chosen to speak on Heart Disease in Infants Under 2 Years of Age because I feel that this is a subject about which most of us need to know more. If this presentation stimulates those individuals already working in the field to find additional answers to the problems, and if it makes the other individuals more aware of what is already known, I will have accomplished my purpose.

There are several ways in which the problem of heart disease in infants might be approached to determine the importance and significance of the subject. Some of the questions to which one would like to know the answers are:

1. What is the incidence of heart disease in consecutive newborn infants?
2. How frequently is heart disease a cause of death in infancy?
3. What percentage of such deaths are due to operable, preventable, and treatable lesions?
4. How frequently is heart disease a cause of morbidity in infancy?

To answer the first question, Green and Apley[1] studied by chest roentgenogram 1,000 consecutive infants born alive at the Boston Lying-in Hospital. In this group of 1,000 infants, cardiac enlargement of a significant degree was present in 16. The fate of these 16 infants is shown in table 1. Death of 7 infants occurred in the neonatal period. A postmortem examination was carried out in only 2 of these infants. An auricular septal defect was found in 1; the other was a case of von Gierke's disease. Nine infants survived, 5 of whom were thought to have congenital heart disease, and 2 had apparent recovery with no signs of any organic defect remaining.

TABLE 1*

16 CASES WITH CARDIAC ENLARGEMENT IN NEONATAL PERIOD

Died in neonatal period; (1 case survived for 2½ months)	7	
Survived:	9	
Inadequate period of observation		2
Congenital cardiac malformations		5
Apparent recovery with normal heart		2

*From Green and Apley, Pediatrics 5:249, 1950.

In order to ascertain an explanation for the reversibility of some cases of cardiomegaly in the neonatal period, Green and Apley[1] also examined the pathologic records of 200 consecutive autopsies on infants born alive at the Boston Lying-in Hospital, but who died in the neonatal period. Cases were selected from this series in which the heart weighed more than 25 gm., a weight considered significantly above the normal by the authors. Using this criteria, 29 of the 200 cases had enlarged hearts. The causes of death in these 29 are listed in table 2.

TABLE 2*

CAUSES OF DEATH IN 29 CASES OF CARDIAC ENLARGEMENT OVER 25 GM.

Group 1	Pathologic lung conditions (intrauterine aspiration, infection, atelectasis, pneumonia)	15
Group 2	Cardiac malformations	8
Group 3	Erythroblastosis fetalis	6

*From Green and Apley, Pediatrics 5:249, 1950.

An unexpected result of the latter inquiry was the large proportion of cases with cardiac enlargement in which some pathologic condition of the lungs was present. It was inferred from this by the authors that milder forms of the conditions described might be compatible with life and with accompanying cardiac enlargement for a period of several months or years.

In answer to question 2, "How frequently is heart disease a cause of death in infancy,?" some information is available on this point as the result of studies by Gardiner and Keith.[2] These authors were primarily interested in the problem of heart disease in the child of school age, but in their paper they also reported data including infants. For general orientation, they reviewed the mortality figures for Toronto, Canada, in the year 1948. Table 3 lists the mortality figures according to etiology from birth to 15 years of age. Of the 508 children, 29 died of congenital heart disease and 5 died of rheumatic heart disease. As seen in figure 1, of the 29 patients who died

Read at the Pediatric Grand Reunion honoring Dr. Irvine McQuarrie on his 25th year of service to the University of Minnesota.

TABLE 3*

CARDIAC DISEASE COMPARED WITH SOME OTHER CAUSES OF DEATH IN TORONTO, 1948, FROM BIRTH TO 15 YEARS

	Deaths in age group	*Percentage of total group*
Total deaths—all causes	508	100.0
Malformations—all types	93	18.3
Congenital cardiac deaths	29	5.7
Probable congenital cardiac deaths	2	0.4
Congenital heart—noncontributory	2	0.4
Rheumatic heart disease	5	1.0
Prematurity	142	28.0
Pneumonia	51	10.0
Birth injury	50	10.0
Leukemia	10	2.0
Cancer—all types	8	1.6
Poliomyelitis	3	0.6
Tuberculosis	1	0.2

*From Gardiner and Keith, Pediatrics 7:713, 1951.

with congenital heart disease, 13 or 45 per cent died in the first 5 days of life and 25 or 86 per cent died under 2 years of age. The types of lesions causing death in the 29 are shown in figure 2. It can be seen that the tetralogy of Fallot and transposition of the great vessels were the 2 most common lesions causing death. Gardiner and Keith apparently had no instances of patent ductus arteriosus as a cause of death in their series. Abbott,[3] however, reported 20 deaths due to *uncomplicated* patent ductus arteriosus

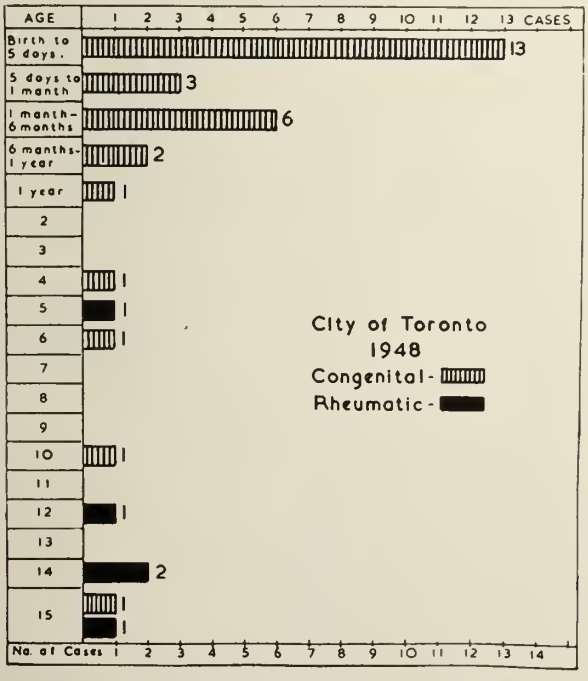

Fig. 1. Deaths by ages, congenital and rheumatic. From Gardiner and Keith, Pediatrics 7:713, 1951.

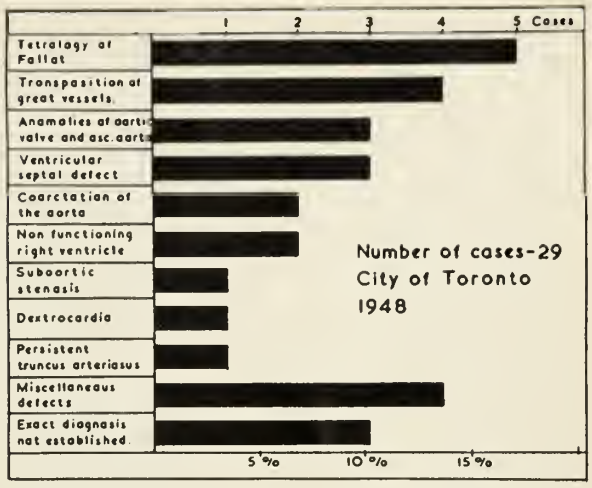

Fig. 2. Congenital cardiac deaths. From Gardiner and Keith, Pediatrics 7:713, 1951.

during infancy from 92 patients dying of this condition. This would be an incidence of approximately 25 per cent. Paul Adams[4] found that in the Minnesota Department of Health Report on Maternal and Infant Mortality for the year 1950, patent ductus arteriosus was listed as a cause of death in 11 of 144 deaths due to congenital heart disease. Thus, we have a partial answer to question 3, "What percentage of such deaths are due to operable, preventable, and treatable lesions?"

While considering the over-all prognosis in congenital heart disease, the report of Maronde[5] is also of interest. In evaluating the incidence of brain abscess in congenital heart disease, he found that between 1938 and 1947, at the Los Angeles County Hospital, 209 autopsies were performed on patients dying with congenital heart disease of all types except patent ductus arteriosus. Of these 209 cases, 128 or 61 per cent were under 2 years of age at the time of death. Only 1 instance of brain abscess occurred in this age group and it was secondary to an otitis media.

From examination of the facts discussed thus far, it can be noted that no comment has been made regarding *endocardial fibroelastosis*. This condition, only recently recognized, as you know, is characterized clinically[6,7] by episodes of left heart failure which have their onset usually between 4 and 6 months of age, left ventricular hypertrophy on the electrocardiogram and roentgenogram, favorable response to digitalis and oxygen, and, in a number of instances, heart murmurs at the apex indicating involvement of the mitral valve. Occasional patients with this condition die suddenly, others only after prolonged illness. Some patients appear to recover

with residual evidence of left ventricular hypertrophy. Pathologically, the endocardium, usually of the left ventricle and left atrium, is markedly thickened by fibrous and elastic tissue elements. It is our impression after talking with interested groups from different parts of the United States that endocardial fibroelastosis is not a rare condition. In fact, it is probably a fairly common cause of cardiac disability during infancy.

Little has been said thus far about rheumatic fever occurring in the infancy period, perhaps justifiably so. Data regarding rheumatic fever in this period is significant by its absence. One instance of rheumatic fever occurring in utero but producing death in the neonatal period has been reported.[8] Some authors have reported patients under 2 years of age who were thought to have rheumatic fever clinically, but who recovered. There appear to be, however, only 10 documented cases of rheumatic fever occurring under 2 years of age in whom postmortem examinations were done and typical Aschoff's nodules were found.[9–12]

The comments thus far might be summarized as follows:

1. Heart enlargement of a significant degree in the neonatal period is not rare if all newborns are subjected to roentgen study.

2. If patients with cardiac enlargement in the neonatal period are followed for several years, some of their hearts return to normal size for no obvious reason. Others, of course, remain enlarged due to congenital heart disease.

3. In studying postmortem material obtained from infants born alive but dying in the neonatal period, a significant group of the infants with enlarged hearts were found to have associated pulmonary disease.

4. In some communities, if not in most, congenital heart disease is a fairly frequent cause of death between the ages of birth and 15 years. In Toronto, Canada, in 1948, congenital heart disease exceeded rheumatic fever as a cause of death by 6 times.

5. Most deaths, over 50 per cent, due to congenital heart disease occur under 2 years of age and a large percentage of them occur in the first weeks of life. According to present information, a significant number of those dying had lesions for which surgery has been developed.

Thus, it appears that in the future the problem of the diagnosis and management of patients with *congenital heart disease* will mainly be concerned with the infancy period from birth up to 2 years of age. Refinements in diagnostic and therapeutic procedures should thus be directed at this level. Likewise, general physicians and pediatricians should be made aware of the potential seriousness of such conditions in the infancy period, so that when signs and symptoms of difficulty due to the heart lesions become apparent, the patient can benefit by such diagnostic and therapeutic procedures as are now available.

Two years ago, before the Northwestern Pediatric Society, Dr. Paul Adams presented in part our experience as a group with the problem of patent ductus arteriosus in infancy. This information was eventually published.[4] Since patent ductus arteriosus is one of the cardiovascular anomalies that can be completely cured or corrected surgically, I think it is worthwhile to review briefly the situation. The original report by Dr. Adams concerned our experience with 16 infants under the age of 18 months in whom surgical closure of the patent ductus arteriosus was thought to be necessary. Since that time our same group has seen an additional 17 patients in the infancy period, which brings the total number of cases to 33. Figure 3 shows the frequency of the clinical symptoms presented by the patients. The majority of infants exhibited

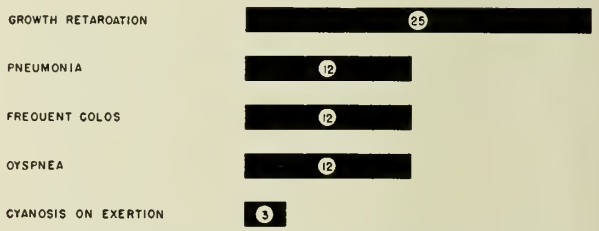

Fig. 3. Frequency of clinical symptoms in 33 infants with patent ductus arteriosus.

poor growth. Nearly one-half had histories of frequent respiratory disease with or without repeated episodes of pneumonia. A number were dyspneic when at rest, and 3 patients became cyanotic on exertion.

Figure 4 shows the frequency of the clinical

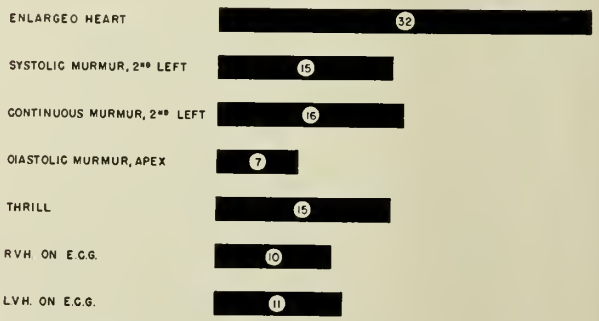

Fig. 4. Frequency of clinical findings in 33 infants with patent ductus arteriosus.

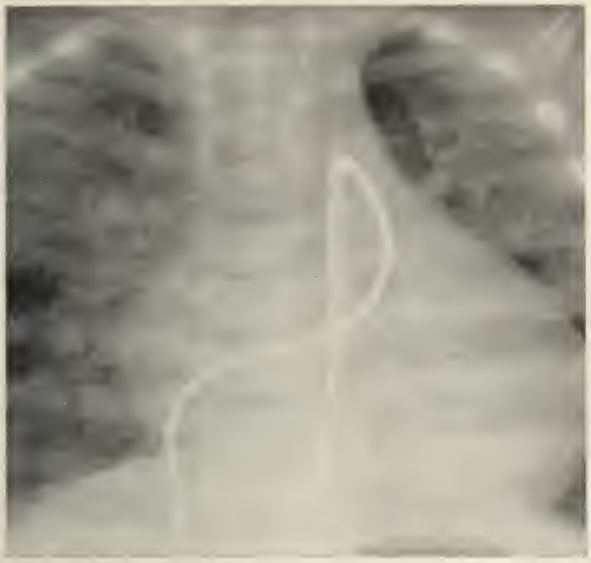

Fig. 5. Roentgenogram showing cardiac catheter proceeding from inferior vena cava, right atrium, right ventricle, and pulmonary artery through the patent ductus arteriosus and into the descending aorta.

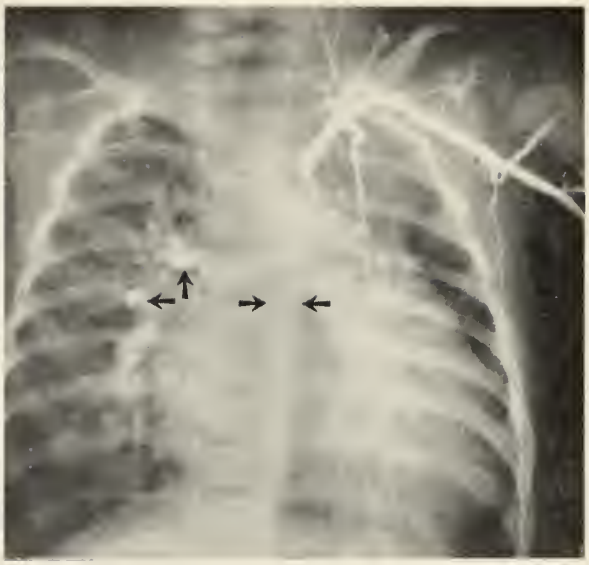

Fig. 6. Roentgenogram showing 70 per cent Diodrast filling arterial system from injection site at brachial artery. Dye simultaneously fills descending aorta and pulmonary arteries as indicated by arrows, thus suggesting a patent ductus arteriosus.

findings in the infants with patent ductus arteriosus. All but 1 had an enlarged heart both on percussion and by roentgen examination. Approximately one-half of the group had only a systolic murmur audible in the pulmonary area. In the remainder, a diastolic murmur was also heard in the same area which in most instances seemed to be continuous. A thrill was palpable in many, and a diastolic murmur heard at the apex was also present in some. None of the patients was in apparent heart failure.

Table 4 shows the outcome of this group of patients. The diagnosis was correctly established

TABLE 4
OUTCOME OF 33 INFANTS WITH PATENT DUCTUS ARTERIOSUS

Number diagnosed clinically only	11
Number diagnosed by catheterization	10
Number diagnosed by aortography	12
Number operated upon for closure	33
Number of deaths	2

in 11 patients based on the clinical findings alone. In 10, the diagnosis was established with the help of a right heart catheterization, and, in 12, with the help of aortography. In many, the ductus was so large and the relationships such that the heart catheter was easily passed from the pulmonary artery to the aorta without difficulty as seen in figure 5, thus confirming the diagnosis. Figure 6 shows the results from a typical aortogram.

All 33 patients were operated upon, employing surgical ligation of the ductus arteriosus. Of these, 2 patients expired during surgery, and at autopsy 1 had endocardial fibroelastosis of the left ventricle as an additional lesion.

This group of patients emphasizes the difficulty which certain patients with patent ductus arteriosus have in early infancy. The atypical nature of some of the physical findings, such as absence of a continuous murmur in the pulmonary area, and evidence of moderate right ventricular hypertrophy is illustrated. The feasibility of surgical correction and the low operative mortality in such infants is also illustrated. The youngest patient to undergo a successful operation for patent ductus arteriosus was 2 months of age.

All that has just been said about infants with patent ductus arteriosus might well be said for infants with coarctation of the aorta and valvular pulmonary stenosis. But time does not permit discussion of either of these latter conditions, nor the problem of paroxysmal tachycardia which frequently is found to occur during this same period.

SUMMARY

The general problem of heart disease in the infant from birth to 2 years of age has been reviewed. Clinical data from infants with patent ductus arteriosus have been presented in an attempt to illustrate a specific condition which can be treated and cured if the correct diagnosis is made. It has been pointed out that future refinements in diagnostic and therapeutic pro-

cedures for patients with congenital heart disease should be concentrated at the infancy period. General physicians and pediatricians should be aware of the potential seriousness of such conditions in the infancy period so that when signs and symptoms of difficulty due to the heart lesions become apparent, the patient can benefit by such procedures as are now available.

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Jimson weed *(Datura stramonium)* poisoning is said to occur as frequently as lead, barbiturate, alcohol, rodenticide, and insecticide poisoning in children. Joe E. Mitchell, M.D., and Fred N. Mitchell, M.D., University of Virginia, Charlottesville, report that the fatal dose is apparently about 4 to 5 gm. of the crude leaf or seed.

Jimson weed grows wild and is found in weed patches and along the roadside throughout the United States and in most parts of Europe, Asia, Africa, and South America. The plant may reach 3 to 6 ft. in height and has a fetid odor. The leaves are large, dark green, sessile, pointed with a deeply indented margin, and have a bitter taste. The flower, which is white and trumpet-shaped, blooms from May to July and produces a 4-valved capsule which contains many tiny, flattened, brown-black seeds with a central attachment.

The alkaloids hyoscyamine, atropine, and hyoscine are contained in every part of the weed, including the seeds. The initial reaction is hyperirritability and delirium which may progress to convulsive movements and terminate in coma. Dilated pupils, intense skin flushing, and extreme excitability are common. Other disturbances include picking movements, incoherent speech, loss of memory, tachycardia, urine retention, and poor visual accommodation. Acute symptoms usually subside within twenty-four to forty-eight hours, but mydriasis may persist a week or more.

When the patient is seen early after ingestion of the weed, gastric lavage with tannic acid or dilute tincture of iodine (30 drops in 1 pt. of water) precipitates the alkaloid remaining in the stomach. During the delirious stage, maniacal behavior and convulsions may be controlled with small doses of short-acting barbiturates or paraldehyde. Stimulants such as Benzedrine may be required for central nervous system depression. Parenteral fluids should be given to maintain water and electrolyte balance.

Joe E. Mitchell and Fred N. Mitchell: J. Pediat. 47:227-230.

Therapeutic Carelessness

MILO G. MEYER, M.D.
Michigan City, Indiana

Patients with long-term illnesses frequently take unbelievable quantities of medicines. In some instances, the illness induced by overmedication and duplication of medicines is far more serious than the original complaint. This problem is of definite importance to the physician as well as the patient, and is rapidly increasing for these rather obvious reasons.

Patients who have been disabled for a long time have a growing tendency to consult not only numerous local doctors, but also major clinics and teaching centers. Such consultations often take place without the family doctor's knowledge and, therefore, without reference by him. In some instances, patients refuse to give a reference since they assume "their doctor" will be insulted if they seek further advice. Duplication of medication is, therefore, a common occurrence. Unless otherwise instructed, the individual is apt to continue his former therapy as well as the new. This represents imperfect patient-physician relationship. It also represents carelessness on the part of the consultant when he fails to instruct the individual to take no medication other than that he prescribed.

Even when only one physician is employed over many years, he has a tendency to change medications frequently in attempts to gain control of the illness. He is often negligent about specifically ordering a discontinuation of previous prescriptions.

Since making it a practice to review medications on each visit, I am continually astonished to find that unless I leave written instructions, almost half my patients with average education and intelligence are confused concerning which medication to stop and which to continue.

The tendency is increasing toward group practice or arrangements for patients' care by certain designated doctors when the attending physician is unavailable. When the patient is informed of this arrangement, he naturally assumes, and too often incorrectly, that a detailed discussion of his specific therapy has occurred. If, then, the substitute physician leaves new prescriptions or medications, the patient usually thinks that his former therapy is also to be continued.

In some hospitals, a common practice is to supply the patient when discharged with his surplus medication, rather than go to the trouble of crediting the bill. The doctor quite naturally may duplicate the prescriptions or even change therapy after discharge. As a result, the patient may be found with digitalis intoxication on the ensuing house call a week later.

There is also the great American pastime of comparing symptoms and diagnoses. If either is identical, apparently quite a normal practice is to exchange prescriptions, on a trial basis at least, and also just as normal to continue their own prescription.

The following examples are, I believe, representative of the usual types of cases in which overmedication occurs.

The first of these pertains to the mother of a physician in a neighboring state; the illness involved was purely psychosomatic. The son, recognizing the nature of the disorder, had written prescriptions at various times for mild sedatives. The doctor in attendance had given sedation of a similarly mild type. When called to see this stuporous patient in consultation, 17 different medications were found at her bedside table, 5 of which were sedatives. As she recovered, she admitted she had taken all of them. The attending doctor actually could not remember whether he had told her specifically to discontinue the previous medication when he prescribed the new, but assumed she should know better than to continue all of them. It was not her business to know this by instinct, but certainly her son, who was a physician, and the attending physician should have done a little investigating.

The following is a list of the contents of a medicine cabinet of an elderly man with cardiorenal failure who had employed 3 home town physicians in the past two years, and who had consulted at a major medical center on his own initiative in that same interval.

The drugs were identified by Rx number, by label, and by laborious telephoning to find the contents of the containers dispensed by the physicians themselves.

MILO G. MEYER, *a 1929 graduate of the State University of Iowa College of Medicine, is a specialist in internal medicine in Michigan City, Indiana.*

Purodigin .1 mg.
Crystodigin .2 mg.
Zymenol
Hydralose fortified
Metrazol tablets
Raudixin 50 mg.
Aminophyllin 3 gr. tablets
Serpasil .25 mg.
Rubraton elixir
Geritol
Aspirin (pink)
Aspirin (coated)
Phenobarbital ½ gr.
Privine nasal jelly
Drilitol spray
Neo Silvol eye drops
Cortone ophthalmic solution
Citrate and belladonna tablets
Kiophyllin

The patient was taking all medications, according to the instructions on the containers, and becoming "worse every day" chiefly with digitalis intoxication and "medication gastritis." It is superfluous to note that he is doing quite well now on 2 medications – digitalis and a laxative.

The next is a list of medicines on the bedside table (figure 1) of a decompensated rheumatic heart disease patient with extreme weakness, disorientation, and extreme malnutrition. She had 2 local doctors in attendance, and had had a consultation at a medical center in the past year.

Crystodigin
Diamox
Mercuhydrin, oral
Theocalcin
Elixir phenobarbital
Ethobral
Thiomerin suppositories

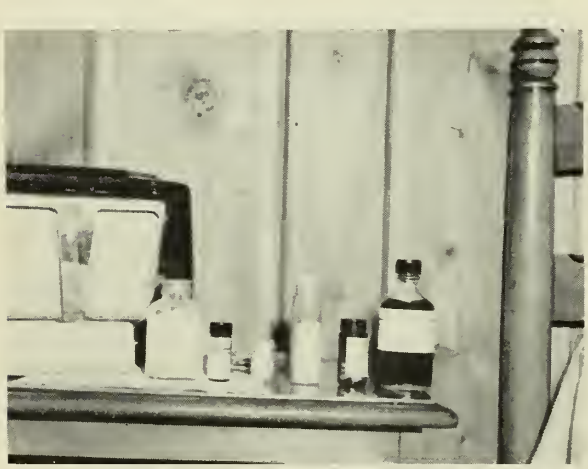

Fig. 1. Bedside table of the rheumatic heart disease patient.

This patient's serum potassium was 3.2 m/e and serum proteins 6.2 gm. with reversal of A-G ratio. After electrolyte balance was restored, she was ambulant in two weeks and taking only 2 medications.

Listed next are the contents of a dresser drawer of a patient with progressive rheumatoid arthritis and massive fluid retention. She has employed 5 different physicians in three years.

Cortef, 20 mg.
Hydrocortone tablets, 20 mg.
Demerol tablets
Salicionyl
Feosol
Butazolidin
Apc with codeine, ½ gr.
Aspirin
Dactil with phenobarbital
Bufferin

All these medications were being given simultaneously to the patient with an average daily cost of $12.00 per day. Although not recovered, she was just as comfortable on only 2 of the 10 being taken.

The last listing is from the medicine cabinet of a patient with chronic and recurrent severe bronchial asthma with only 1 doctor in attendance. Other medications were found in a small fruit basket in the basement!

Elixir Propadrine, Orthoxicol
Tedral
Quadrinal
Nethapryn
Copyronil
Pro-Banthine
Cortisone tablets
Rau-Sed
Nephenylin
Benadryl
Hycodan
Aminophyllin suppository
Nembutal
Ammonium chloride
Norisodrine Aerohalor Cartridge
Ephedrine in oil nasal spray
Benzidrex inhalor
Hypo for adrenalin injections
Toryn syrup

This case obviously represents therapeutic desperation. It is also significant to note that no detailed allergic work-up had been attempted. This patient greatly improved later after hyposensitization to and avoidance of discovered allergens.

These cases are used since they present rather dramatic illustrations of the present trend to try any and all of the new drugs. They also illustrate the points used in the following summary.

SUMMARY

1. Changing attitudes of patient-physician relationships are becoming a therapeutic hazard.
2. Even the individual doctor cannot remember which medications he has given to a patient during a long-term illness.
3. It is impossible to know which medications the patient is taking on his own initiative, or which he may have exchanged with his friends.
4. Sometimes drugs given by previous attending physicians are impossible to identify.
5. All drugs not identified can be discarded.
6. Time can be taken to carefully review with the patient on each home or office call the medicines being taken.
7. Certainly the obligation of the attending physician is to protect his patient against reduplication of drugs, unnecessary expense in therapy, and, finally, drug poisoning.
8. It is within the province of the physician in almost all cases to tell the patient what his medications are, their expected favorable reaction, and the possibilities of side or toxic effects. By so doing, greater confidence will be attained and the dangers mentioned in this article will be avoided to a great extent.

Lancet CLINICAL REVIEWS

This department of THE JOURNAL-LANCET *is devoted to reports on cases in which all the appropriate diagnostic criteria have been employed, the best known treatment administered and the results recorded. It is desired that these case reports be so prepared that they may be read with profit by physicians in general practice, hospital residents and interns and may be of considerable value to junior and senior students of medicine. This department welcomes such reports from individuals or groups of physicians who have suitable cases which they desire to present.*

Anemia Associated with Myxedema

JOHN F. BRIGGS, M.D.
St. Paul, Minnesota

MYXEDEMA may be complicated by anemia. The anemia is either hyperchromic or hypochromic in type. The mechanism producing the anemia in myxedema is not known. However, failure to recognize the fact that the thyroid dysfunction is the causative factor of the anemia often leads to chronic invalidism. Recognition of the myxedema and therapy directed toward this condition brings about an adequate hematologic response.

CASE REPORT

A 23-year-old white male was referred to the hospital because of an intractable anemia. His story dates from May 1952 when he became tired and weak. He attributed his fatigue to the loss of sleep and the excessive amount of time spent in school activities. In June 1952, his friends told him that he looked pale. By this time he noticed that he was lazy and lacked "all pep." In November 1953, he attempted to donate blood to the Red Cross but was rejected because of anemia. He was seen by his family physician who informed him that he was suffering from anemia and treated him with routine hematinics. A slight response to the use of these drugs occurred, but in general his condition remained static. In the last three months, the patient noticed that he was very sensitive to cold and that he was losing his hair. When seen on January 11, 1954, he had a typical myxedematous appearance. The blood pressure was 112/76, pulse 72, and temperature 98.2° F. The physical examination was completely negative except for partial alopecia of the scalp, loss of hair from the eyebrows, and from his legs.

Laboratory examination at this time revealed a hemoglobin of 9.5 gm., a red blood count of 3,850,000, and a white blood count of 6,550 with a normal differential count. The reticulocyte count was 0 per cent, and the platelet count was 180,000. The urine examination revealed traces of albumin and the presence of red blood cells. The urea nitrogen was 24.5 mg. per cent, the icterus index 9.5 units, and the blood cholesterol was 330 mg. The basal metabolism was −49 per cent, and a second test was −28 per cent. A study of the blood smears revealed nothing of note. Hemolyses began at .42 per cent and was complete at .32 per cent. This was within normal range. The phenolsulfonphthalein test was 50.5 per cent excretion, and dilution and concentration tests varied from a specific gravity of 1,002 to 1,017. Stool examinations were negative, the Wassermann test was negative, and the tuberculin test revealed a 1+ reaction. The agglutinations for undulant fever were negative. The Thorn test showed a normal response, and the 17-ketosteroid determination was within normal limits.

Roentgen examination revealed a normal intravenous urogram, and a routine chest film was normal. Electrocardiographic tracings were normal.

In view of the coexisting myxedema, the anemia and the renal changes were thought to be part of the hypothyroid state. Sternal bone marrow studies were not performed because the patient had been receiving large amounts of liver as well as other hematinics. He was placed on 1 gr. of thyroid daily. He also received 2 capsules of Extralin three times daily. On this therapy, his condition improved rapidly. Growth of hair increased on the scalp, eyebrows, and over the lower extremities. The cold intolerance disappeared, and he no longer became fatigued but could carry on his normal activities. On April 24, 1954, the basal metabolism was −19 per cent, the hemoglobin was 12.5 gm., and the red blood count was 3,990,000. On August 7, 1954, the basal metabolism was −17 per cent, the hemoglobin remained at 12.5 gm., his hair was completely restored, and all of the previous urinary findings had disappeared. On January 8, 1955, the basal metabolism was −15 per cent and the hemoglobin was 13.2 gm.

CONCLUSION

A case is presented of a patient who was suffering from myxedema which was complicated both by anemia and renal involvement. Emphasis is placed upon the fact that both the renal changes and anemia in myxedema are often reversible when the myxedematous condition is successfully treated by thyroid extract.

JOHN F. BRIGGS, *a 1929 graduate of the University of Minnesota, is clinical associate professor of medicine at the University of Minnesota.*

Notes from a Medical Journey

Cagliari, Sardinia

Dear Jay:

A week has gone by here in Cagliari and we can account for 91 men studied in detail in the lab while the clinicians, Drs. Paul White, Reuben Berman, and the Italians have surveyed the hospitals. We are doing the dietary work, anthropometry, physical examinations, and paper electrophoresis of the blood serum here but the final cholesterol analyses are being done in Naples and in Minneapolis. Fresh serum goes to Naples by the night boat and the paper strips go by air mail to the Stadium Laboratory so we shall end up with measurements of the total serum cholesterol and the proportions of the cholesterol in the alpha and beta lipoproteins. Henry Taylor, aided by his wife, is running a detailed ballistocardiographic study on all of the subjects. The electrocardiograms are going to Ernst Simonson in Minneapolis for the quantitative analysis.

We have lots of local help so the program here should not be too arduous, but our Sardinian colleagues are so assiduous with their hospitality that our time is filled with feverish activity from 8:00 a.m. until late at night. Mr. M. Aresu, the professor of medicine, is extremely cordial and generous and we are elegantly set up in the brand-new blood bank building which has not yet started regular operation. Across the street is the fine new building of the Medical Clinic (150 beds) and immediately behind us tower the great stone walls of the old fortified city. These ancient walls are, of course, a thousand years younger than the Roman city of Nora across the bay, while Nora, in turn, started nearly two thousand years after the building of the prehistoric "nuragi" -- the huge stone village fortresses of the early Sardinians which are scattered all over the island.

But I should retrace a few items of the last few weeks before I get lost in four thousand years of history. Nobody knows what the early Sardinians ate -- though I suspect the diet was lower in fats than our current diet in the states! Nor does anyone know what their medical problems were. One thing is sure; the men who built the nuragi were a good deal further advanced than the primitive Bantu and Zulu we left behind us in Africa two weeks ago.

The flight from Cape Town to Durban is about as far as from Chicago to New York but the coast of the Indian Ocean below us, with the mountains of the "Hottentots Holland" inland, could not be mistaken for the shores of Lake Michigan. When we landed at dusk it was like a mild Turkish bath after the gentle coolness of the Cape. Dr. Gale, the dean of the Medical School at Durban, met us at the airport and rushed us to the hotel for a hasty bite and a bath before my lecture. There was a good audience, with a reception and tea following, and the local doctors crowded around to tell me how rare coronary heart disease is among the Zulu who, like the Bantu we had studied in Cape Town, live on a very low fat diet.

Visits to laboratories and clinics (Drs. Ted Gilman and Sidney Kark) started early the next morning, but our host had saved the afternoon for an exploratory drive over a fantastically bad road through the Zulu reserve. Dr. Gale learned Zulu before he learned English so we had a fine time, stopping to chat with diviners and witch doctors and to admire a fancy "hair-do" or fine set of anklets on the women passing by. And as we charged up and down the mountain sides of the Valley of a Thousand Hills, we talked about the problem of providing medical services for some 10 million Bantu, Zulu, and Bushmen. At least it appears they need not worry about coronary heart disease nor are peptic ulcer, appendicitis, or thrombo-embolic phenomena common. As the sun sank lower, we stopped time and again to inquire whether the track we were on would eventually bring us out of the reserve onto any road to Durban, but no one knew for sure and by then we were beyond retreat. Anyway, we <u>did</u> catch the night 'plane for Johannesburg, there to change 'planes for the long (over 5,000 miles) flight to Athens by way of Nairobi and Khartoum.

Dr. Theodore Tsaltas, just back after several years at the Rockefeller Institute in New York, met us in Athens and we dashed around furiously, clambering over the Acropolis, drinking thick coffee and the ancient type of Greek wine that tastes of pine needles, all the while discussing future research. Tsaltas is promised a grant from the Williams-Waterman Fund which I am supposed to superintend from afar. The idea is to find out what happens to people who habitually eat a high-fat diet with almost all of the fat coming from olive oil. In parts of Greece, on the Island of Crete, for example, it appears that dinner consists of a piece of bread and a bowl of olive oil with maybe a bit of fish, swimming in olive oil, for Sunday.

Somehow by 2:00 p.m. the next day we were in Rome, agreeing that the new British "Viscount" turbo-prop is about the best 'plane now flying and that the transition of almost 80° of latitude in a day and a night is all too confusing. It is spring here in Italy while at Cape Town, fall was too far advanced for comfortable swimming. Certainly it was hot enough en route at Khartoum for a swim but it was four o'clock in the morning and the 'plane stopped less than an hour, barely time enough for our two Norwegian fellow passengers to have a few rounds at the bar. They were harpooners flying back from the end of the Antarctic whaling season, and they responded to my greeting in Danish by mumbling their pleasure that they were already in Copenhagen and where was the streetcar to the bars and restaurants of Tivoli?

At Rome were Henry and "Cay" Taylor and Dr. Alfonso del Vecchio, a former student of mine, and Dr. Alberto Fidanza, Flaminio's brother, and bad news about a delay in getting the ballistocardiographs through the customs and then we were in Naples happily greeting Dr. Flaminio Fidanza and his mother and father and many old friends with the good news that all the lab equipment was through the customs and quick let us pack up to catch the boat to Sardinia. Just before boat time Dr. Paul White arrived from the States and Dr. David Rutstein, of Harvard, passing through on another job, joined us for lunch together with the Dr. Vittorio Puddu family who had driven Paul down from Rome. So at 4:00 p.m. we sailed off into the sunset, "Mare Nostrum" as calm as our own Lake Owasso, and we relaxed in the knowledge that we were still actually on the schedule planned many months ago with every prospect of getting the data in Sardinia we needed.

Our Bologna colleagues, Drs. Poppi, Postelli, and Franco joined us at Cagliari with the blessings of their chief and our good friend Professor G. Sotgiu and here we are. Margaret is comfortably ensconced as chief of the chemical lab; both of Henry Taylor's ballistos are working well; hordes of assistants rush around fetching and carrying and washing glassware; a steady stream of subjects is ushered in; and the blood flows freely. It is too early to say much about results, but it is clear that the local diet is low in fats and that coronary heart disease is not very common. Paul White, Reuben Berman, and the rest of the clinical team bagged a good case of angina pectoris and a fresh infarct in the first day's "hunting," but since then only 2 more coronaries have been found in some 200 medical patients. All in all, it seems like Naples last year, that is midway between men in Minnesota and the Bantu in regard to both diet fats and the incidence of coronary heart disease. On Monday we start with coal miners at Bacu Abis, an hour's drive from here, and there we may find the diet to be still lower in fats.

Dr. R. Sanna Randaccio has a nice clinic there and is the sole doctor for the community of 5,000 people, most of whom, apparently, he knows by their Christian names. In the last few years he has had only a single case of myocardial infarction and less than half a dozen cases of angina pectoris! But we shall see.

Paul White and I have only a few days left. In the meantime, I have lectures and conferences in Ancona, Rome, Geneva, and Lund, Sweden, so a few more people will be reminded about Minnesota. I expect to be home by the time Margaret, the Taylors, and Dr. del Vecchio start the job of checking the good people of Bologna who gorge on a relatively high fat diet (around 30 per cent of calories from fats) and apparently suffer the consequences in atherosclerosis. But that story, as well as many other interesting questions, including the use of tobacco, will have to wait for another letter.

We all send the best of wishes to you and our good friends back home in Minnesota.

As ever,

Ancel Keys

The Journal Lancet

SERVING THE MEDICAL PROFESSION OF MINNESOTA, NORTH DAKOTA, SOUTH DAKOTA AND MONTANA

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Better Health for Your Children. A Medical Guide for Parents, by I. Newton Kugelmass, M.D., 1955. New York City: McGraw-Hill. 341 pages. $4.50.

This book was written to help parents understand their children in health and disease. The chapters on retarded children are particularly good, as would be expected, since Dr. Kugelmass is especially interested in that field of medicine. Other interesting chapters include subjects such as the care of the sick child, the care of the diabetic child, and the many diseases of children.

Walter C. Alvarez, M.D.

•

Correlative Neurosurgery, by Edgar A. Kahn, Robert C. Bassett, Richard C. Scheider, Elizabeth Caroline Crosby, and 11 contributors, 1955. Springfield, Illinois: Charles C Thomas. 388 pages. $19.50.

As the title implies, the authors of and contributors to this book have presented a volume of information and suggestions which will be of everyday, practical use to the physician who comes into contact with neurosurgical patients. It is not intended to be an exhaustive treatise on neurosurgical diagnosis, treatment, or operative technic.

Diagnostic procedures are touched upon lightly throughout the book except for the three topics of electroencephalography, isotope encephalometry, and routine skull roentgenography. A separate chapter is devoted to each of these subjects, presenting a good basic review of each as it applies to neurosurgical conditions.

The body of the text is dedicated to the diseases which make up the bulk of a large neurosurgical practice: brain tumors, brain abscesses, spinal cord tumors, developmental anomalies, central nervous system trauma, vascular lesions of the central nervous system, and surgical pain problems. Each of these topics is considered in turn by either an author or contributor, who imparts to the reader a useful resumé of the subject with readable reflections upon the problems involved. Many intelligent, practical suggestions are offered regarding handling of neurosurgical cases, which have largely been born of extensive experience accumulated on the neurosurgical service of the University of Michigan Hospital.

Deserving special mention are the serveral sections entitled Anatomical Considerations by Elizabeth Caroline Crosby included in the chapters on Gliomas of the Cerebral Hemispheres, Tumors of the Sellar Region, Tumors of the Third Ventricle, and Tumors of the Posterior Fossa. These sections consist of reviews, brief and understandable, of the fiber tracts and other structures likely to be involved by neoplasms in the areas mentioned. These explanations are directed primarily toward providing an understanding of the symptomatology produced by tumors in various locations.

The authors have achieved their purpose of correlating contemporary principles of neurosurgery. Excellent bibliographies are supplied for the reader who desires details not included in the text.

Howard C. Chandler, M.D.

BOOK REVIEWS

•

The Medical Care of the Aged and Chronically Ill, by F. Homburger, 1955. Boston: Little, Brown & Company. $5.75.

Intended for practitioners, medical students, nurses, and intelligent laymen concerned with the many problems of patients with advancing age and chronic illness, this book may be read with profit by those to whom it is addressed. Dr. Homburger presents some eminently practical advice on the management of conditions that all too frequently receive little attention in schools of medicine and nursing.

The choice of subject matter is excellent, with the more common medical causes of disability and the more frequent complications of chronic illness receiving appropriate emphasis. Especially welcome are the chapters on osteoporosis, a common and often neglected condition among elderly people, and the chapter on hemiplegia, which is a good summary of the management of this condition.

It is, of course, quite impossible to produce a book covering the subjects of chronic diseases and geriatrics without provoking some dissent on minor points from others interested in these fields. The present reviewer, for example, finds little to commend the distinction between "conventional" therapy and "modern" treatment.

Probably no two physicians agree on what constitutes a "minimal" health inventory, but routine glucose tolerance tests and determinations of protein-bound iodine would be included by few internists. Moreover, there appears to be little reason to have routine laboratory determinations of both urea nitrogen and nonprotein nitrogen (p. 9).

Not all rheumatologists consider gold therapy for rheumatoid arthritis to be out-moded (p. 40), nor do they all agree that "all patients (with rheumatoid arthritis) are definitely entitled to a therapeutic trial (with hormone therapy")) (p. 44). Not all urologists agree that Gram stains of the urinary sediment are of "key importance in the diagnosis of urinary infections" (p. 181). Physiatrists do not consider heat to be an "adjunct to physiotherapy" (p. 233), but rather one of the integral components of this kind of treatment.

Raoul Dufy's sketches are indeed "unique documents." They are decorative and artistic, but not especially useful as illustrations. In the author's study, these would be superb; in his book, more informative illustrations would be preferable.

Despite these controversial comments, this book is a welcome addition to the libraries of those interested in chronic diseases and geriatrics, and it can be warmly recommended.

Frank W. Reynolds, M.D.

•

The Action of Insulin, by Niels Haugaard, PH.D., and Julian B. Marsh, M.D., 1953. Springfield, Illinois: Charles C Thomas. $3.75.

This monograph attempts to summarize the present knowledge of the action of insulin, although accepting the fact that the precise biochemical mode of action of insulin remains unknown. Essentials of intermediary metabolism are discussed as well as the chemistry of insulin. Despite considerable information about the structure of insulin, probably as much as any protein, chemists cannot yet relate this knowledge to its physiologic action. It is interesting that there are differences in the relative amounts of amino acids in insulins isolated from various species. The physiology of insulin action is regarded in terms of the processes involved in the regulation of the concentration of the glucose in the blood. The most important metabolic defects in diabetes are con-

(Continued on page 30A)

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(Continued from page 28A)

sidered to be in the synthesis of fat and the utilization of carbohydrate. Theories of insulin hypersensitivity and of insulin resistance are discussed. Experiments are quoted indicating that, in the combination of insulin with muscle, the usual metabolic effect occurs. This excellent monograph is intended for those who are curious concerning recent investigations.

C. A. McKinlay, M.D.

•

Adaptive Human Fertility, by Paul S. Henshaw, Ph.D., 1955. New York City: McGraw-Hill Book Co. 322 pages. $5.50.

The other day the reviewer read that in a country such as India the widespread application of modern methods of preventive medicine would save the lives of millions of children and others who now die of infestations by innumerable parasites and pathogenic bacteria.

The author went on to say that if this country protected most of the children now being born from an early death, thereby enabling them to grow into adult life, millions would soon die for lack of food. We know that throughout history, when men have run short of food they have overrun their borders, attacking and killing their neighbors.

As a few wise persons have said of late, unless the Japanese people learn to use the technics of contraception, some day another terrible war will occur, as the land of Japan is already carrying about as many people as it can support.

For all of those persons who have enough sense and freedom from indoctrination to be able to face these facts, and to wonder what might be done about them, Dr. Henshaw's book is a must. Dr. Henshaw started out as a biologist and then became a human ecologist, a man who studies the growth of population and the numbers of persons who can be supported on a certain amount of land. Having gone to Japan after World War II, to work with the Japanese leaders in trying to determine what can be done with the mounting population pressure, he became very much interested in this problem.

He has since worked with the United States Public Health Service. In this work, he has watched in several countries the miracles worked in the field of public health, with the upsurge in population growth and the bewilderment that comes to people already greatly afflicted by overpopulation and the resultant poverty and undernourishment.

Dr. Henshaw deals with each phase of the subject showing great knowledge of the literature and of the problems as he has studied them. Very interesting is Dr. Henshaw's chapter discussing the possibility of controlling ovulation or conception with the help of some hormone or other drug, either taken by mouth or inserted into the vagina.

He says that, some day, some such protective substance may be found. Unfortunately, androgens or other such drugs are not satisfactory because of their unpleasant side reactions. The reviewer wishes space permitted descriptions of all the fine chapters in the book. Dr. Henshaw speaks of the emotional and religious conflicts that arise when it is suggested that people restrict the number of their children so that all may have enough to eat. He tells of the methods used to avoid conception, and he discusses the future of this problem. As he says, it is sad that most people know nothing about the problem, and many of those who do know refuse to do anything about it, while still others try to prevent the hungry people from studying and attempting to solve the problem.

Walter C. Alvarez, M.D.

American College Health Association . . .

Notice has been received from the secretary-treasurer, Mrs. Ruby Rich Burgar, Occidental College, Los Angeles, of the nineteenth annual meeting of the Pacific Coast Section of the ACHA held at the Samarkand Hotel, Santa Barbara, December 2 and 3, 1955. The University of California at Santa Barbara, Goleta, was the host institution.

The program included the following panel discussions: "Selecting Mentally and Physically Fit Candidates for Teaching Credentials," "The Specialist Considers the Common Dispensary Complaints," and "What Can the Students Contribute to a College Health Program?" Students from the University of Washington, Stanford University, the University of California at Berkeley, and the University of California at Los Angeles participated in the latter panel discussion.

* * * *

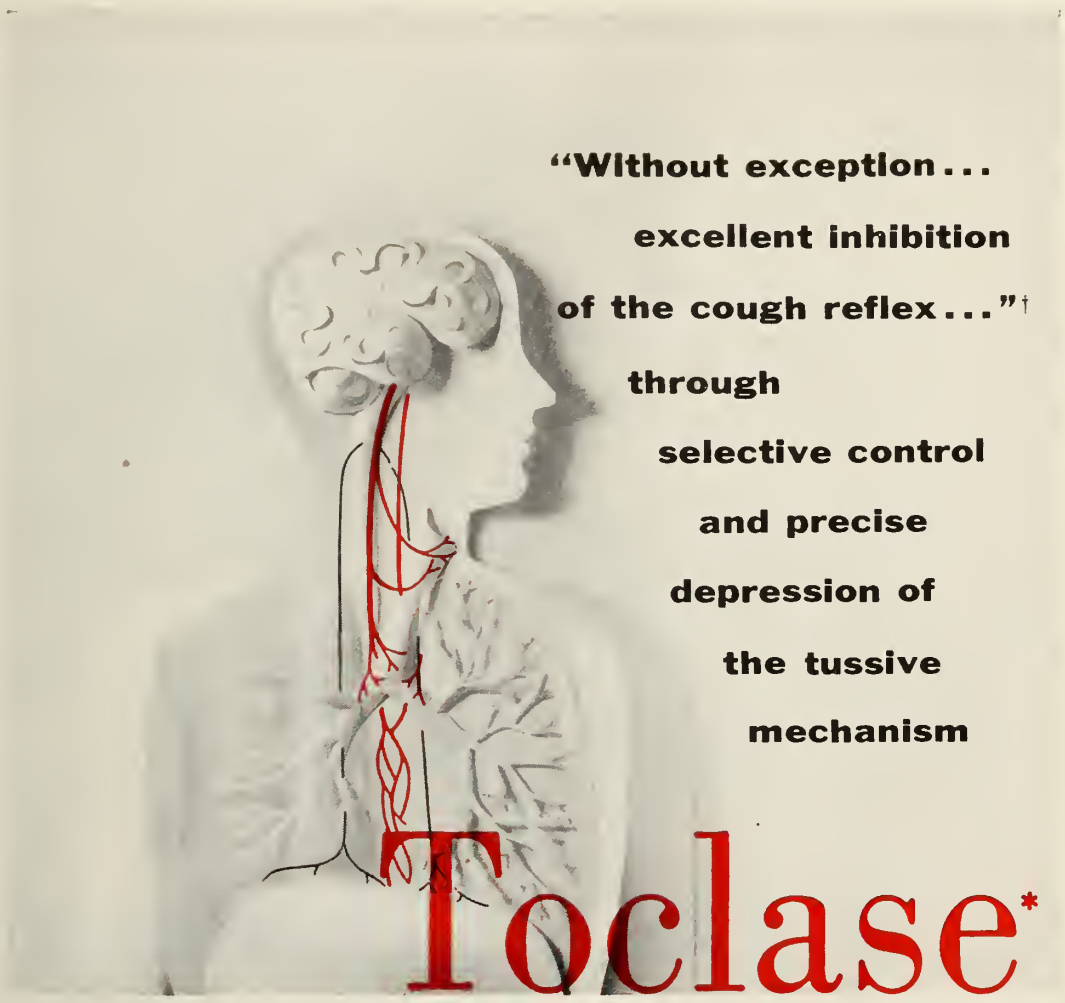
During the middle of October after a meeting of the National Board of Medical Examiners in Philadelphia, the president of the ACHA, Dr. John W. Brown, traveled around the country to attend to association business. Conferences were held with Dr. Bruce Roxby of Temple University, chairman of the Local Sections Committee; Dr. Irvin W. Sander, secretary-treasurer, at Wayne University in Detroit; and with Dr. Ruth Boynton at Minneapolis, chairman of the Local Arrangements Committee for the next annual meeting. Dr. Brown reports that work is well along on a program for the next meeting to be held in Minneapolis May 17 through 19 with the University of Minnesota as host.

* * * *

Dr. Joseph Edward Raycroft, first chairman of the department of physical education and athletics at Princeton University and one of the founders of the American College Health Association (president 1922 and 1923), died on October 1. He was 87 years old.

Dr. Raycroft was a graduate of Rush Medical College in 1899 and remained at the University of Chicago as professor of hygiene until 1911 when he went to Princeton as director of physical education and athletics. Here he became known as the "father of intramural athletes," and by the time he retired in 1936 he had developed the broad athletic program in which over 90 per cent of the

(Continued on page 32A)



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†Parish, F. A.: M. Times *83*:870 (Sept.) 1955.

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student body participates. The Joseph E. Raycroft "Athletic-Medical" Library was organized and named for him on the campus in 1948.

Dr. Raycroft received many honors and served in various capacities as a physician in addition to his work at Princeton. In World Wars I and II, he served as consultant to the government on Training Camp Activities and Physical Fitness. He received an honorary Master of Physical Education from Springfield College. He served on several hospital boards in New Jersey, and was a former president of the board of managers of the New Jersey State Hospital for the Insane.

The early records of our association are filled with the evidence of Dr. Raycroft's interest and work in the field of college student health. The present strength and professional status of the ACHA are largely the result of the groundwork done by Dr. Raycroft and the other members of the founding group. It is sad to report his death.

° ° ° °

Dr. C. G. Menzies, director of Health Service at Michigan State University, East Lansing, announces several additions to his staff. Dr. Byron Casey of Detroit has accepted the post of head of the psychiatric division and Charles Bouterse of Grand Rapids, Michigan, has been added as the third psychiatric social worker.

Dr. C. J. Poppen and Dr. Cameron D. Keim have joined the medical staff, making a total of 6 in that department.

Construction on the new addition to the Health Service at Michigan State University began on December 1 and is expected to be completed in about a year. Dr. Menzies has indicated that plans of the new addition will be sent to the office of the ACHA for inclusion in the book of building plans which is lent on request to member institutions.

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Dr. Grace Hiller, Goucher College, Baltimore, officially represented the ACHA at the National Conference on Intramural Sports for College Men and Women, held in Washington, D.C., October 30 through November 2, 1955.

° ° ° °

Memberships on both standing and special committees of the ACHA for the year 1955-1956 are practically complete, according to Dr. John W. Brown, president. Following is a list of ACHA committee membership:

Administration – chairman: Ralph I. Canuteson, M.D., University of Kansas; William E. Taylor, M.D., Southwest Missouri State College; Leona B. Yeager, M.D., Northwestern University; Herbert R. Glenn, M.D., Pennsylvania State University; Donald S. MacKinnon, M.D., University of California, Los Angeles; Muriel Farr, R.N., Bryn Mawr College; Bruce S. Roxby, M.D., Temple University; and J. Wilbur Armstrong, M.D., Berea College.

Editorial Committee – chairman: Irvin W. Sander, M.D., Wayne University; Ruth Boynton, M.D., University of Minnesota.

Environmental hygiene – chairman: Richard G. Bond, Ph.D., University of Minnesota; Marcus Powell, University of Iowa; Tom Gable, University of Nebraska; Fred Ingram, University of California, Berkeley; Walter S. Mangold, University of California, Berkeley; Paul H. Visscher, M.D., Montana State University; Gayle Pond, R.N., Western Michigan College; and John B. Butler, Harvard University.

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Faculty Medical Care — chairman: Llewellyn Sale, Jr., M.D., Washington University; John E. Sawhill, M.D., New York University; Murland W. Fish, M.D., University of Washington; W. R. Mason, M.D., Emory University; James L. Weiler, M.D., Knox College; D. W. Lafene, M.D., Kansas State College, Manhattan; and Glenn R. Leymaster, M.D., University of Utah.

Health education — chairman: A. O. DeWeese, M.D., Kent State University; W. Roy Mason, Jr., M.D., Emory University; Elmer Werner, M.D., University of Cincinnati; and Edward J. Dvorak, Ph.D., University of Minnesota.

Health service and physical activities — chairman: John G. Grant, M.D., Iowa State College, Ames; Frances Wiese, M.D., Mount Holyoke College; Donald Cowan, M.D., University of Minnesota; Donald Petersen, M.D., St. Olaf College, Northfield, Minnesota; Charles Lester, M.D., University of Washington; Patty Groves, M.D., Mount Holyoke College; L. W. Holden, M.D., University of Colorado; and Fred Miller, M.D., University of Oregon.

Local arrangements — chairman: Ruth Boynton, M.D., University of Minnesota; and Edward Dvorak, University of Minnesota.

Local sections — chairman: Bruce Roxby, M.D., Temple University; Irvin W. Sander, M.D., Wayne University; Donald MacKinnon, M.D., University of California, Los Angeles; Ruth Boynton, M.D., University of Minnesota; Glenn Leymaster, M.D., University of Utah; Gilbert Coltrin, M.D., Associated Colleges, Claremont, California; Margaret Zeff, M.D., University of California, Berkeley; Robert H. Vadheim, M.D., University of Florida; and Samuel I. Fuenning, M.D., University of Nebraska.

Mental health — chairman: C. Douglas Darling, M.D., Cornell University; Robert Hinckley, M.D., University of Minnesota; J. Wheelright, M.D., University of California, Los Angeles; Lewis Barbato, M.D., University of Denver; Vernon E. Keye, M.A., Wayne University; Saxton Pope, M.D., University of California, Berkeley; and William I. Brill, M.D., Lincoln, Nebraska.

Nursing services in college health departments — chairman: Muriel Farr, R.N., Bryn Mawr College.

Records — chairman: Dana L. Farnsworth, M.D., Harvard University; Gilbert Coltrin, M.D., Associated Colleges, Claremont, California; and Leona Yeager, M.D., Northwestern University.

Research — chairman: John Summerskill, Ph.D., Cornell University; William Lester, M.D., University of Chicago; John W. Brown, M.D., University of California, Berkeley; Paul O. Greeley, M.D., University of Southern California; William Hausman, Major, MC, U.S. Army Hospital, West Point; John P. Monks, M.D., Harvard University; William E. Taylor, M.D., Southwest Missouri State College; and Jean A. Curran, M.D., State University of New York, Brooklyn.

Tuberculosis — chairman: Max L. Durfee, M.D., Oberlin College; Ralph I. Canuteson, M.D., University of Kansas; Otto J. Keller, M.D., Northern Illinois State University, DeKalb, Illinois; Charles Lester, M.D., University of Washington; Gertrude T. Huberty, M.D., University of California, Los Angeles; and William M. Brace, M.D., University of Michigan.

Advisory committee — Drs. J. Arthur Myers, Esmond R. Long, Floyd Feldmann, Robert J. Anderson, J. Edward Johnson, and J. Burns Amberson.

Special committee on increasing membership — chairman: Samuel I. Fuenning, M.D., University of Nebraska; and Richard Wise, M.D., Columbia University.

Special committee to study the financial structure of the ACHA — chairman: Norman S. Moore, M.D., Cornell University.

News Briefs . . .

North Dakota

MINOT'S VETERANS ADMINISTRATION HOSPITAL is progressing toward a goal of full-scale operation. The one-ward limitation order was recently rescinded and permission has been granted to open a second 40-bed ward. More nursing technicians are needed before the second ward can be opened. The present patient load averages around 45 daily, having grown from a low point of 12 last June. The four key men at the institution are Drs. Walter L. Dumond, F. I. Bloise, Maurice Bakalienik, and Carl A. Carlson, the hospital's dentist.

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THE MICHIGAN CLINIC in Nelson County Memorial Hospital opened late in October. The clinic is staffed by Dr. T. A. Osten, Mrs. Osten, R.N., a registered x-ray and laboratory technician, and a receptionist. Additions to the clinic include an automatic dry writing electrocardiogram, waterless basal metabolism, equipment for blood chemistry, serum and blood typing for blood transfusions, a new microscope, centrifuge, and a Van Slyke apparatus for alkaline or acidity of the blood. Treatment at the clinic is by appointment, but emergencies supersede.

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DR. T. H. HARWOOD, dean of the University of North Dakota School of Medicine, was elected a director of the North Dakota Cancer Society at the group's annual dinner in Fargo.

° ° ° °

DR. FRANCIS A. JACOBS, assistant professor of biochemistry at the University of North Dakota School of Medicine, has been awarded a research grant of $4,310 by the North Dakota Cancer Society. The grant will be used for a new technic, developed by Dr. Jacobs, to determine the rate of absorption of proteins from the intestinal tract.

° ° ° °

DR. C. M. LUND, scientific director of the North Dakota State Cancer Society, was presented with a Certificate of Merit for his years of service in cancer scientific work at the recent meeting of the North Dakota Cancer Society.

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DRS. ROBERT D. SCHOREGGE, Bismarck; WILLIAM O. WEBSTER, Fargo; and DAVID B. HORNER, Minot, were among those inducted as fellows into the American College of Surgeons at the organization's recent five-day clinical congress in Chicago.

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DR. O. P. ERICKSON, physician and surgeon, recently established practice in the Southside Shopping Center at Fargo. Dr. Erickson spent more than seven years as an officer in the armed forces, and for one year was assistant professor of physiology and pharmacology at the University of North Dakota Medical School.

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DR. W. LOREN FENNELL, a specialist in surgery, has joined the Crosby Clinic staff. Dr. Fennell graduated from the University of Manitoba Medical School, had three years of postgraduate work in England, and was Commandant of a medical training center in India for three years. He has practiced in Cooperstown isnce 1951.

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