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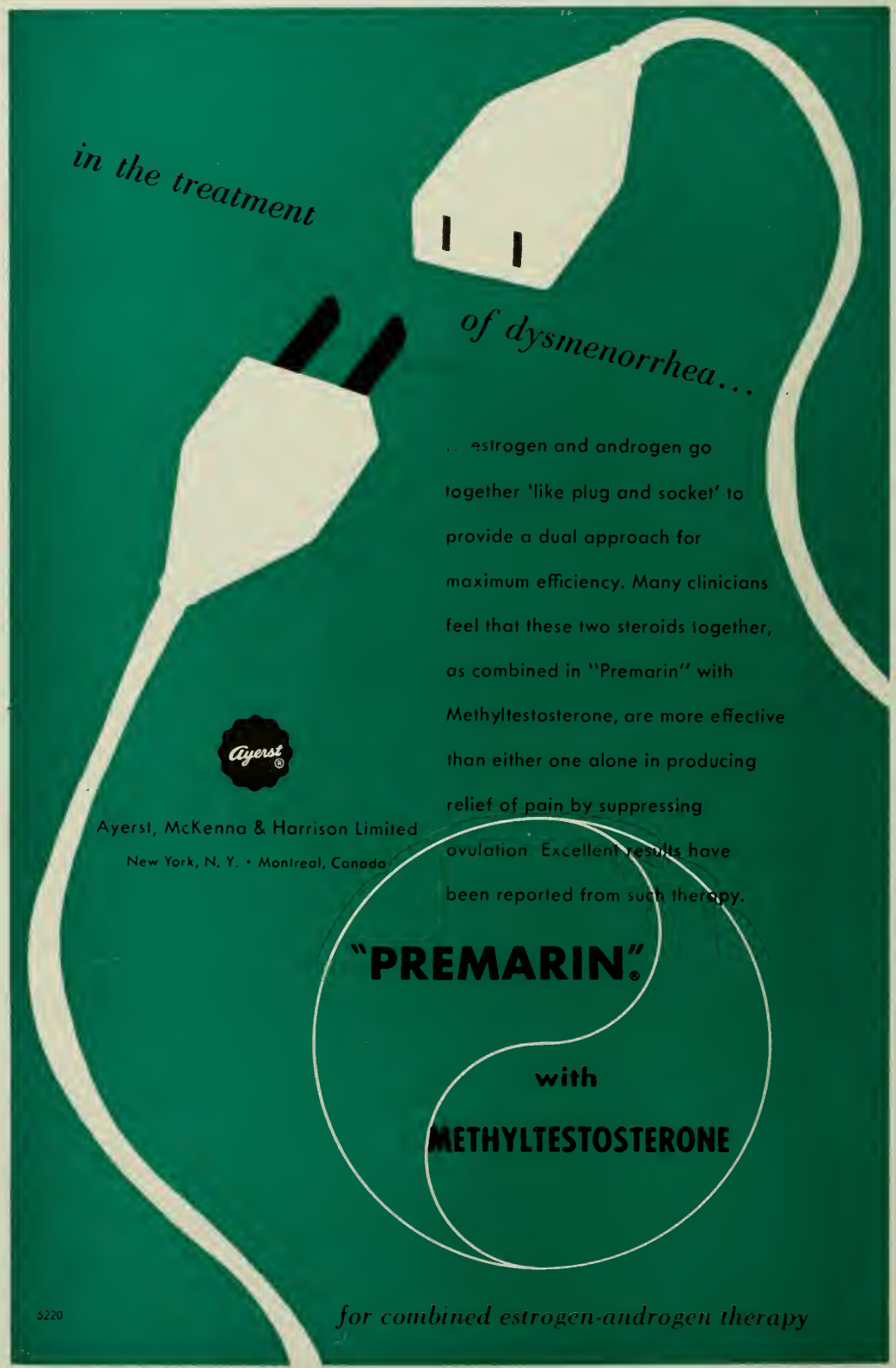
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Crime and the Doctor*

KEITH SIMPSON, M.D.
London, England

THE PART played by the doctor who is called to help in the investigation of deaths in uncertain or suspicious circumstances is an important one, and I need make no excuse for discussing his duties before an audience consisting of university staff, pathologists, practicing doctors, and a leavening of lawyers, for these are matters of concern to us all.

The doctor is likely to be the first scientifically trained person to attend the scene, and the decisions he makes may be vital to a proper understanding of the case—and to an absolutely fair treatment of other people whose interests may become involved. It is as well to remember the mischief, if not grave injustice and danger to liberty, that may follow from indifference or ignorance in coming to any decision on "a dead body."

There are three principal duties to be discharged: to establish whether death has, in fact, taken place (and, if possible, to say when), to decide whether or not it is proper to issue a certificate, and to recognize any medical cause for suspicion of foul play. Each is of vital importance, and only a doctor can provide safe answers to these issues.

HAS DEATH, IN FACT, TAKEN PLACE?

Though no doubt about this may arise in most cases—indeed the body may be mummified or dismembered—it is essential that the doctor should actually examine the body to assure himself of the fact; it is not enough to assume death. Not long ago I was asked to perform an autopsy on a woman whose cold stiff body had been found exposed on a common. She was certified dead, as she lay under blankets in an ambulance, by a doctor who contented himself with putting a hand on the skin. She was taken to the mortuary, stripped, and placed on the table for necropsy, where she was shortly after seen to be swallowing and undoubtedly also breathing: she survived some seven or eight hours in hospital. Extreme cold, grave loss of blood and shock, vagal inhibition as from immersion in cold water, and electrocution may all simulate death so closely that great care is necessary to avoid this shocking error.

Stethoscopic examination for the heart sounds is the only really reliable test: if there is no heart beat for four or five minutes eventual survival is impossible. Groping with throbbing fingers for a thready pulse can be deceptive, and testing for the breath with a feather or cold mirror are gestures that can only waste vital time. If the doctor is in doubt, or there is difficulty because of noise of traffic or other inconvenience, he should certainly institute resuscitative measures and then have the body removed to a place where it can be examined under better conditions. Resuscitation should not be relaxed until no possible hope of survival exists: striking

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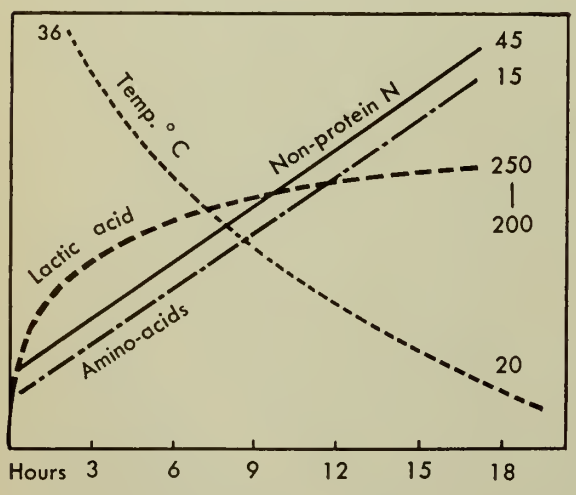
*A lecture presented at the meeting of the Minnesota Pathological Society at the University of Minnesota May 20, 1952.

recoveries have ensued after long periods of apparently suspended animation in cases of electrocution.

As a corollary to this first decision the doctor may be asked how long ago death took place. No more difficult medico-legal task has ever existed, and no doctor can do more than give an approximate time. The temperature of the body is a useful guide in the first 24 hours, and this simple test of cooling should not be forgotten, even if the body feels cold, as it may be some 18 to 20 hours before it is actually as cold as its surroundings. For this purpose skin temperatures are unsuitable, and the thermometer should be inserted into either the rectum or a hole made in the abdomen. Some 2° F. (1.1° C.) an hour is the normal rate of loss for a body in the open air in average English weather, but less than 1° F. (0.55° C.) an hour may be lost in bed or when heavily clothed, and as much as 3 to 4° F. (1.7 to 2.2° C.) an hour in cold weather: the circumstances will plainly affect the rate of heat loss.

Some recent work by Schourup in Scandinavia has reduced the margins of error in the measurement of temperature as a basis for estimation of the lapse of time since death. He has shown (see graph) that measurement of the lactic acid, amino acids and non-protein nitrogen in the cerebrospinal fluid affords a correcting factor for the temperature change when the formula shown in figure 1 is used.

Rigor mortis is an uncertain guide but should, of course, be assessed, as it carries the time limit set by cooling from about 24 hours to about 36. The working rule that rigor, starting in the face at six hours, is complete to the feet and hands at 12 hours, stays for 12 hours, and takes a third 12 hours to pass away is a fair general guide. Rigor is, however, too uncertain to be safe. After 36 hours another basis of estimation—the development of decomposition and its spread into the body from the flanks of the abdomen—goes on slowly and with many vagaries, depending on the initial bacteriology of the bowel; it is largely controlled by climatic conditions. Cold water doubles the rate of cooling and delays rigor and decomposition to the same degree (figure 2).



$$T = 36 - ax\,T^{\circ} + \frac{\text{antilog } \frac{LA}{180} + \frac{NPN\text{-}15}{16.7} + \frac{AA\text{-}1}{7.35}}{4}$$

Fig. 1. Formula determining lapse of time after death.

CERTIFICATION OR NOT?

If a doctor has been in attendance during the last illness—preferably within several days—and knows the cause of death to be natural, he has a statutory duty to issue a certificate of death for the registrar.

If he has not attended during the last illness,

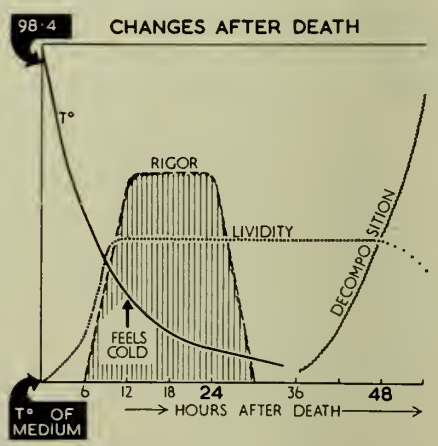


Fig. 2. Chart showing the major changes by which the lapse of time after death might be estimated.

or if he has any doubt about the cause of death or knows (or suspects) it to be unnatural or associated with injury or violence of any kind (or date), he will only obstruct the public interests by issuing some kind of certificate which will either divert inquiry or will take vital time to pass through the hands of the registrar before being referred to the coroner. Where suspicion of crime arises, however faint the scent of foul play, the doctor should, of course, lose no time in informing the police (who may be left to inform the coroner) so that police inquiries may start without delay. In England a doctor is not compelled by any regulation to report cases to the coroner—the registrar is the official sorter—

but only harm can come of deliberately trying to avoid inquiry: obstructing the coroner in the discharge of his duties is, in fact, punishable by imprisonment or fine (or both).

The classes of cases to be referred to the coroner consist, from the practitioner's point of view, of:

1. *Deaths the causes of which are unknown or uncertain*—all cases seen only after death.

2. *Violent or unnatural deaths,* or deaths which might, from the doctor's knowledge, be related to: (a) accident or injury of any date; (b) want, exposure, or neglect; (c) poisoning—by drugs or poisons of any kind; (d) abortions if in any way suspicious, and suspicious infant deaths; and (e) industrial hazards.

3. *Deaths before full recovery from anesthesia* or suspected to be connected with operative or other treatment.

Important litigation issues may thereby be clarified while the material is still fresh and suitable for study. It is as well to anticipate litigation and questions.

MEDICAL CAUSES FOR SUSPICION

The last duty of a doctor confronted with a dead body is to decide, using his training in medicolegal matters, whether there is any cause for suspicion of suicide or foul play, or whether circumstances and any injuries that may be seen are capable of some simple natural explanation.

It is, of course, no part of a doctor's duty to be a detective, and he must on no account interfere with the setting of a scene which the police may later have reason to examine with meticulous care, to photograph, and to search for fingerprints. He should therefore tread warily and avoid touching anything smooth that might carry prints. A doctor can ascertain the fact of death, insert a thermometer (registering to zero) either into the rectum or into a hole made in the abdomen, and observe superficial injuries, loss of blood, smell or stains of poison, signs of asphyxia, and so on without disturbing the body. He should not let the body be moved if there is any reason for uncertainty, far less real suspicion; he must, however, not fail to make a reasonably painstaking examination before deciding this point.

A doctor, called to a house to see the dead body of a girl in bed, looked into the room and saw she lay there covered by the bed-linen up to the mid-neck. He did nothing more, but later informed the coroner of a "sudden death" unattended by him in life. On the coroner's officer making his routine visit for inquiry and turning down the sheets it was evident that the girl had been strangled (figure 3). Her mother was found upon search of the house under the stairs, also strangled. Valuable time had been lost in a murder hunt.

In another case a doctor, called to certify the death of an elderly woman patient in a nursing home, failed to see the asphyxial petechiae in the face and conjunctivae which later resulted in the matron being charged with murder—by suffocation with a pillow during an argument.

Fig. 3. Marks of strangling by a piece of string not observed by the doctor called "to see a girl found dead in bed" because the doctor did not trouble to examine the body. Serious delay in police inquiry resulted.

The recognition of grounds for suspicion, apart from the plainest pedestrian circumstances of murder, rests largely with the doctor's ability to recognize suicide when he sees it. The classical suicidal cut throat, with its tentative incisions, elective site, curve, and slope; the solitary or doubled stab over the heart, without "protective" wounds to the hands; the contact discharge of a firearm in one of the elective suicidal sites—center brow (figure 4), temple, roof of the mouth, or over the heart—these are all traditional suicidal events that the doctor has been trained to recognize instantly. He may also recognize the

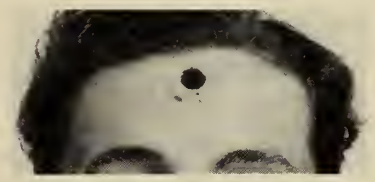


Fig. 4. Typical suicidal firearm entry wound — a contact discharge set in one of the "elective" sites. A 32-cal. revolver was lying near the right hand.

suicidal nature of a cut throat which is done with the help of a mirror, the significant grasping of a weapon by cadaveric spasm as it was at the moment of death, and the careful preparation of a coal-gas suicide to prevent ventilation—the circumstantial features that may support his medical findings. He is entitled to use these things to help him evaluate a case.

It is when these classical suicidal features are absent—when the throat wound does not follow the rules or is accompanied by protective hand wounds, when the firearm wound is in an inaccessible part of the body (figure 5), or where there is some similar cause for uncertainty—that the doctor must go cautiously. Perhaps some

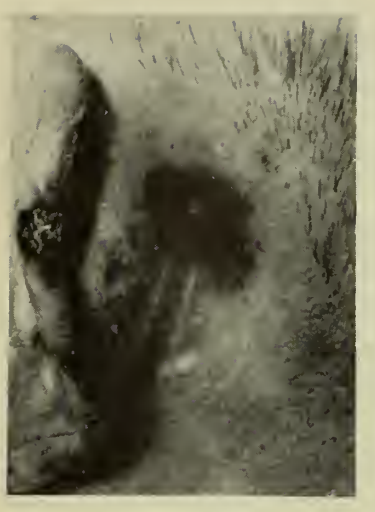


Fig. 5. Typical homicidal firearm wound set behind left ear. No weapon at scene.

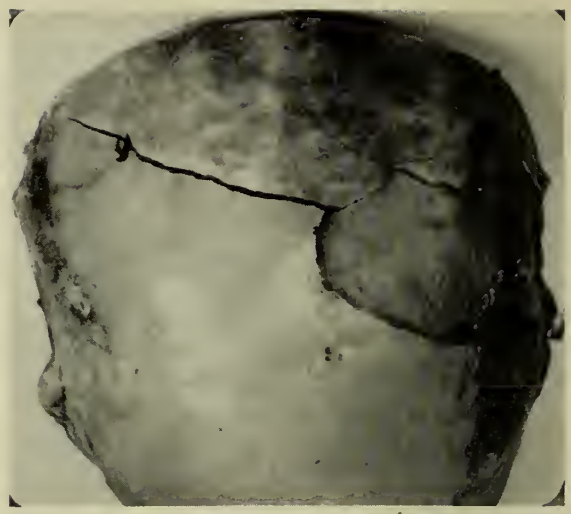


Fig. 6. Suspicious head injury. Fracture of skull, showing significant shaping of depressed area. Suspicion of foul play was allayed by revising the scene.

accident is responsible, but only careful inquiry can decide such things, and this inquiry is outside the doctor's province.

When the medical findings are equivocal a doctor is entitled to know what the circumstances were, for special alternative explanations of some wound may exist. A man with a blunt head wound may have had some machinery fall on him or have been thrown pitching on to the head, or have been struck with some blunt weapon: it *is* important to know whether he was working on the docks among loading gear or lying in bed at home. A doctor should certainly obtain all the relevant information he can when injuries of an equivocal kind are present.

A man last seen in loud argument with fellow workers at the entrance to the factory was found dead in the same spot on the ground, alone, about one and a half hours later. He had a head wound (figure 6) which could have resulted from a vicious kick from the toe of a boot, but examination of a projecting piece of ornamental stonework at the gate showed some fragments of cuticle and several head hairs identical with the dead man's. He had marked coronary atheroma, and it was realized that if he were to collapse from this (after heated argument) he could well have sustained the otherwise suspicious head wound which he bore.

The full facts are often enough to throw an entirely new light on the medical observations, often to dissipate suspicion, and a doctor need never hesitate to ask what is known so far in order to form a more definite opinion. It is remarkable how much more one sees of a case when it is ultimately argued between opposing counsel before judge and jury at a trial—a trial of possibilities. Every doctor should have an alert and open mind not readily given to always accepting the first obvious explanation of an event, though not, at the same time, stubbornly refusing to accept a reasonable possibility. Medical evidence should always be carefully reasoned and, therefore, reasonable.

Deaths from grave injuries by the roadside should not arouse suspicion until the possibility of a vehicular street accident has been altogether excluded. Bodies found dead in a busy river may be expected to bear injuries sustained after death from passing craft, crabs, or recovery gear. The mutilated victim found in the yard of a block of flats is as likely to have fallen from a higher floor or the roof as to have been "beaten up." The suffocated body lying face down in the pillow is not unlikely to be that of an epileptic, and infants quite often meet their death as a result of turning their faces into the bedding: their position and deep asphyxial coloration need not arouse suspicion of foul play, though it would be wise never to overlook the possibility.

IDENTITY PROBLEMS

Though not commonly the lot of the ordinary doctor in practice, identification problems are not rare and a brief account of them may provide some matters of special interest to the pathologists and anatomists who are in the audience.

Some are pedestrian and could well be solved by the schoolboy. A 9-inch windpipe, with lungs attached but no tongue or heart, could hardly belong to a human victim, and a sheet of stomach as large as a bath towel, found in Epping Forest, might equally be assumed to be beyond the capacity of even a well trained bar man.

At the other extreme—in the Haigh (acid bath) case in London we found three gall stones, a few eroded bones, probably female, and—fortunately—undissolved acrylic resin dentures with porcelain teeth which established the identity of the well-to-do widow victim.

A classic reconstruction of crime occurred in my practice in London during the war years when disintegrated bombed remains were not uncommon and suspicion was, therefore, likely to be lulled.

The Baptist Church Cellar Murder. R. v. Dobkin. In July, 1942, the dismembered, partly burned, remains of a woman identified at once as such by the uterus (enlarged by a fibroid tumor) which lay in the exposed pelvis—were discovered by demolition workers under a cellar floor at the rear of a disused bombed Baptist church in Vauxhall, London. The conditions, bearing in mind the character of the debris in which the body was found, suggested *burial for twelve to eighteen months.*

The head was detached from the trunk, but complementary with it, and parts of the arm and legs, together with the lower jaw, were missing. A minute fragment of scalp with hairs lay stuck to the back of the head, but search of some three tons of the debris in the cellar floor failed to reveal any other human material. A yellowish powder, which proved subsequently to be slaked lime, lay over the tissues, which were almost dry, especially the head and neck regions; it had been sprinkled over the body to keep down the smell or accelerate the disintegration of tissues, but had, of course, preserved them.

Reassembly of the body showed it to be about 60¼ to 60¾ in. in stature. Allowance had to be made for missing lower leg and foot bones and for soft tissue. Pearson's formulae, used with the remaining intact long bone (L. humerus) as a basis, gave an estimated height of 5 ft. ½ in. to 5 ft. 1 in. and the less reliable Rollet tables gave the stature as 4 ft. 10½ in. to 4 ft. 11 in. (It was later given in evidence by a sister that the dead woman, then identified, was 5 ft. 1 in. or "about her own height" (which was 5 ft. 1 in.).

Coloring was provided by the tag of hair, which was dark brown, aging, going grey. *Age* was estimated from the condition of closure of the skull vault sutures, and the palate suture (closing at 45 to 60 years) as being about 40 to 50.

At this stage the police were therefore informed that the remains were those of a woman, 5 ft. to 5 ft. 1 in. in height, with dark brown hair, going grey, aged 40 to 50, *with a fibroid tumor of the womb,* who was likely to have met her death some 12 to 18 months previously: *teeth were available in the upper jaw* to further the identification if dental records could be traced.

The police had ascertained, in the meantime, that the wife of the fire-watcher to the Baptist church premises had disappeared without explanation fifteen months previously (April 11, 1941). She had last been seen in the company of her husband whom she was pestering for arrears of maintenance. She was 5 ft. or 5 ft. 1 in. in height, with dark brown hair going grey, aged 47, and had refused medical attention at two London hospitals (where records were traced) for a fibroid tumor of the womb. Her dental surgeon was traced and produced a record of the condition of the upper jaw as he last saw it. The upper jaw of the victim was identical in respect of shape, residual teeth, fillings and denture fitting marks: it showed, on x-ray, residual roots in the correct regions.

Superimposed photography as first practiced in the Ruxton case was presented to complete the identity data.

Dobkin, who as fire-watcher was the only person with access to the cellar in question, had had a fire there during the night of April 15th, four days after Mrs. Dobkin had disappeared. It had been *drawn to his attention* after some two hours by a passing constable, and the prosecution suggested that Dobkin had been endeavoring to dispose of the dead body of his wife and that the fire had got beyond his control. The remains showed fire burns at several centers. Bags of lime similar to the sample on the body were found in the fire-watchers' premises next door. Dobkin had no proper explanation for the fire and later tried to deny knowledge even of the existence of the cellar.

Among the tissues preserved by the lime were the thyroid cartilages which showed dried bruising around a fractured superior cornu of the right ala. This provided the only evidence on which to suggest that death was due to strangulation by the hand, the only likely cause for such a stray fracture, and the opinion was not strongly contested by the defense. Dobkin was charged with murder, convicted at the Old Bailey, and executed.

The doctor who carefully assesses the fact of death, indicates approximately how long ago it occurred, offers a reasonable explanation of the medical findings, and encourages caution in disturbing things unless he is satisfied foul play can be excluded will not expose himself to abuse or ridicule in court, nor will he be likely to commit significant error. Crime and suicide must be recognized without delay, and the doctor's elementary forensic training, together with common sense, will not often let him down in these matters. Where accident seems likely or the position is equivocal a cautious sifting of possibilities *pari passu* with the police inquiry is more likely to achieve the correct solution and to avoid wrecking the scene.

"The most commonplace crime is often the most mysterious because it presents no new or special features from which deductions may be drawn."

Conan Doyle: *A Study in Scarlet*

Splenic Cysts*

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Cysts of the spleen are of relatively rare occurrence. Only four cases were reported by Pemberton[1] in approximately 800 splenectomies, or an incidence of 0.5 per cent. It is perhaps the rarest form of cystic disease in the abdominal organs. Over a period of 114 years since the first description of cystic spleens, only 163 cases have been published in the medical literature. They are classified as single or multiple, unilocular, multilocular, parasitic or non-parasitic, true or false, primary or secondary, hemorrhagic, serous or lymphatic. The most common type is that of false cysts, a true cyst being less frequent. A true cyst of the spleen has a specific, secretory lining which may be epithelial, endothelial or parasitic. False cysts possess only a dense hyalin or fibrous tissue wall or a layer of condensation of adjacent splenic tissue. McClure and Altemeier's[2] classification, generally accepted as the most complete and informative, is as follows:

I. *True cysts*—lined by specific, secreting membrane
  A. Epithelial
    1. Dermoids
    2. Epidermoids
  B. Endothelial
    1. Lymphangioma
    2. Hemangioma
    3. Polycystic disease
    4. Some serous cysts
  C. Parasitic—lined by a protoplasmic matrix containing numerous nuclei
    1. Hydatid cyst—caused by Echinococcus
II. *False cysts*—no specific, secreting lining
  A. Hemorrhagic
  B. Serous
  C. Inflammatory
    1. Acute necrosis and infection
    2. Chronic tuberculosis
  D. Degenerative liquefaction of the capillaries caused by embolism or arterial thrombosis.

Echinococcus cysts occur about twice as frequently as all the various forms of true non-parasitic cysts. False cysts are encountered approximately four times as often as the true type. Eighty per cent of the false cysts are large, solitary and unilocular. Two-thirds of them are the hemorrhagic variety and one-third the serous type. Women appear to be most often affected, particularly during the child-bearing age. Most of the cases occur between the ages of twenty and fifty. Trauma seems to play an important role in the formation of the large hemorrhagic or serous type. Many of these are more properly described as encysted hematomata due to injury which fails to produce a laceration of the surface of the spleen, but which causes tearing of the vessels in the interior of the organ resulting in gross hemorrhage. It is conceivable that intrasplenic hemorrhage may also occur spontaneously without antecedent trauma. Some believe that the transformation of the hemorrhagic cyst to a serous cyst occurs, although in most instances patients with serous cysts give no history of trauma. The interval between the history of trauma and the formation of cysts varies from one to forty years in reported cases. Eighty per cent of the hemorrhagic cysts can easily be traced to accidents of different kinds, but the fact that the patient has undergone some trauma does not prove that the cyst itself was traumatic in origin. Fowler[3] believes that the most rational explanation of many hemorrhagic cysts is infarction and secondary hemorrhage with cyst formation following an embolus. He also believes that trauma may be a factor and lists this possibility in 25 per cent of the cases. Emphasis is placed on the fact that large spleens are more apt to be injured, thus malaria and syphilis are predisposing diseases. The only parasite giving rise to cysts of the spleen is Echinococcus granulosis.

There has been considerable conflict in the literature regarding the ability to diagnose splenic cysts. Some authors state that preoperative diagnosis of splenic cysts has rarely been made. One group could find only one case of splenic cyst which had been diagnosed roentgenologically

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before operation. However, Sweet[5] states that large cysts of the spleen present a clinical picture which is so characteristic that diagnosis can be readily made. The subjective symptoms that the patient presents are usually those of pressure sensation in the left upper quadrant and occasionally a complaint of tumor mass with some slight pain in this area. A dragging sensation or heaviness in the left hypochondrium and epigastrium may also be noted. There may be pain referred to the left shoulder and occasionally digestive disturbances. The most important problem, however, is one of mechanics due to displacement of adjacent abdominal organs. Examination usually reveals a large, abdominal tumor mass in the left upper quadrant, which on careful palpation is round, smooth and without evidence of a splenic notch. The mass extends toward the left iliac crest and toward the right side of the abdomen. The left costal margin is usually pushed outward by the tumor which also extends beneath it. This, as a rule, does not occur in pancreatic cysts and rarely in ovarian cysts. The lower border of the tumor, even when large, does not occupy the pelvis the way an ovarian cyst does. That the tumor is cystic can often be determined by the sensation of resiliency imparted on bimanual palpation. A definite fluid wave can often be detected in large cysts. The roentgenological evidence can, as a rule, be considered diagnostic. The left side of the diaphragm is high and under the fluoroscope the motion is impaired. A plain abdominal plate shows a large, soft tissue mass arising in the left upper quadrant. The lower pole of the shadow may have an angular, almost pointed contour that extends downward and to the right into the pelvis. This observation depends upon the fact that when the cyst occurs in the upper pole of the spleen, a triangular lower pole remains at the lower extremity of the tumor. Conversely, if the cyst should occur in the lower pole, this finding of a triangular area doubtless would not occur. After a barium meal the stomach is found to be pushed to the right; and if the cyst is large, it is pushed backward as well. The colon, especially the transverse and splenic flexure and descending portion, is found displaced downward and to the right. The left kidney, as visualized by intravenous pyelogram, is shown to be pushed downward by the tumor. The contour of the kidney pelvis is usually not altered. However, there is some controversy upon these diagnostic points and in some instances of splenic cyst; the kidney has been reported to be displaced upward. Other observers mention the fact that pyelograms readily rule the kidney in or out of consideration. Occasionally pressure on the left kidney may produce deformity of the calices and confuse the picture with findings suggestive of urinary tract lesion. Some believe that pancreatic cysts, omental cysts, mesenteric cysts and cysts of the left lobe of the liver cannot be differentiated. To add to the confusion, Benton[4] states that downward displacement of the splenic flexure of the colon is almost pathognomonic of a large cyst of the spleen. He feels that the correct diagnosis is readily made prior to operation. One other differential diagnostic possibility is that of calcified aneurysm of the splenic artery. The differential diagnosis between an aneurysm and a splenic cyst is extremely important from the surgical standpoint, as operation on an aneurysm of the splenic artery may be a hazardous procedure with a high mortality. The presence of a bruit will usually serve to differentiate the two.

The following are reports of two cases of splenic cysts diagnosed preoperatively.

Case 1. M. K., female, age 17, single. Patient stated her father and mother were living and well, as also were her two brothers and two sisters. One brother had jaundice. Her past illnesses included jaundice at the age of 13, chickenpox and measles. Significant history was that she fell from a moving car when 3½ years old. She states that there were no noticeable injuries at that time. Menses are normal except for dysmenorrhea for the first two days of period.

When seen on February 9, 1949, her chief complaints were frequent headaches, usually in the forehead and occipital areas and usually at the end of the day. No other eye, ear, nose and throat symptoms, except for some photophobia and burning in the eyes. On cross examination it was found that for about three months her appetite had been poor, and was accompanied by dyspepsia for rich foods and occasional vomiting. There was no hematemesis and stools were normal. Some epigastric pain of a vague character had been noted intermittently. Belching was a distressing problem. Patient had lost 20 pounds in the last four months. There were no cardiovascular symptoms except for dyspnea on exertion. No genito-urinary symptoms were noted. The patient was a well developed and well nourished white female, weighing 162 pounds. Blood pressure was 120/80.

The entire general physical examination was negative except for a mass in the left upper quadrant that extended approximately three fingers below the left costal margin. It had a smooth border and appeared to be rather deep. No splenic notch could be found. The pelvic organs were normal by rectopelvic examination. Urinalysis was negative. Hemoglobin was 13.75 grams with the red blood cell count being 5,000,000. The white blood cell count was 6,800; the platelet count was 180,000. Differential showed polymorphonuclears 53 per cent, lymphocytes 39 per cent and eosinophils 8 per cent. The chest x-ray was negative except for some elevation of the left diaphragm. Cholecystography

showed a normally functioning gallbladder. The barium meal showed marked displacement of the stomach toward the right abdomen. A soft tissue mass measuring roughly 18 by 21 centimeters was shown occupying the left upper quadrant. Its lower border was convex. The left kidney was in a lower position than usual with its inferior margins at the level of the fourth lumbar vertebra. Intravenous pyelography showed prompt excretion of the contrast material. The right renal pelvis, calices and ureter were normal. The mass in the left upper quadrant was interpreted to be separate from the kidney, but appeared to be causing pressure upon its superior pole, as usually found in a retroperitoneal mass rather than a spleen. It is unusual for a spleen to cause such renal pressure.

Additional studies revealed: bilirubin—direct 10 minutes, 0.6 mg.; direct 30 minutes, 0.9 mg.; total indirect, 2.1 mg. per 100 cm. The bromsulfalein test was 7 per cent. Blood urea 36 mg. Albumin 4.7 grams. Globulin 3 grams per 100 cm. Fragility test showed beginning hemolysis 0.44 per cent; complete at 0.34 per cent. A control test was the same. Prothrombin time was 100 per cent. Agglutination tests for typhoid, paratyphoid and undulant fever were negative. Serology was negative. Bone marrow puncture was done on February 17, and showed granular cell and erythroblastic hyperplasia. The myeloid-erythroid layer was 15 per cent.

Splenectomy was performed on February 19, 1949. The pathological specimen weighed 1,619 grams and measured 29 by 24 by 22 cm. (figure 1). It was globular in shape and presented a tense surface. The surface contained two irregular light yellow areas suggesting a healed lesion, measuring 5 cm. and 3 cm. across, respectively. On section a large cyst-like space was encountered which almost completely replaced the parenchyma. It contained 750 cm. of chocolate colored fluid. On the surface of the fluid were glistening particles. On microscopic examination the lining showed smooth muscle with a layer of lymphocytes in which were numerous microscopic blood spaces. The inner surface presented white trabeculations. Histological examination of the cyst wall showed it to be a dense, fibrous tissue infiltrated with numerous lymphocytes. Hemorrhagic cyst of the spleen was the final diagnosis.

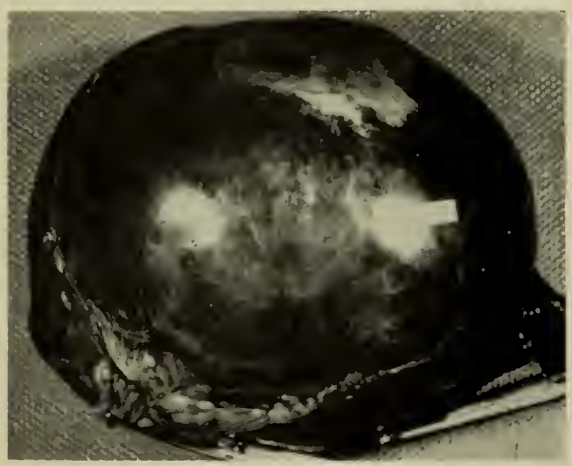

Fig. 1. Large splenic cyst causing almost complete parenchymal replacement.

Case 2. Mrs. D. P., age 51. Patient was seen in January 1950 because of varicose veins. She had had a thyroidectomy in 1948, and a hysterectomy in 1946. On questioning she stated that she had noted some epigastric pain of a mild and vague nature with spells of belching. A full meal especially distressed her. On examination a mass in the left upper quadrant was palpated and thought to be an enlarged spleen. Hemoglobin was 12.4 grams; white blood count 5,900. X-ray examination of the left upper quadrant showed a mass which displaced the stomach and colon. A distinct calcified wall could be seen measuring 8 cm. in diameter. Calcium was scattered throughout the area. A barium enema revealed a medially displaced descending colon. The mass appeared to be attached to the colon. Preoperative diagnosis was cyst of spleen apparently attached to and displacing the descending colon.

A splenectomy was performed in March 1950. The specimen consisted of an enlarged spleen measuring 3½ by 4½ by 17 cm. (figures 2 and 3). The upper pole contained a large cyst which measured 7½ centimeters in diameter. Unfortunately this cyst had been ruptured before the spleen was weighed. The cyst contained 500 cm. of cream-colored, cloudy fluid without which the spleen weighed 220 grams. The cyst wall was smooth and tough and averaged 1½ mm. in thickness. Examination of the cyst fluid revealed the following: specific gravity, 1028; microscopic examination: few red blood

(Continued on page 40)

Fig. 2. Splenic cyst occupying upper pole.

Fig. 3. The same cyst opened, showing a smooth fibrous wall.

Regional Coordination Helps Small Hospitals*

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REGIONAL COORDINATION can be of great value to small hospitals. This value cannot be measured accurately at the present time since this is a relatively new concept. A great number of examples of regional coordination exist; however, only a few approach a comprehensive program and many have been in operation but a short time. The regional programs which have been put into operation, however, have produced evidence to show that they are practical and profitable enough to warrant serious consideration of widespread use of this vehicle for the improvement of hospital services and the reduction of the costs of hospital care.

Perhaps it would be well to begin with a definition of terms. We know of no formal definitions which are in general usage so the interpretations which will be used in this discussion are given so that they may not be misunderstood.

Regional coordination means any coordinated effort by a group of hospitals in the same general geographic area. This does not necessarily imply any formal delineation of the region or a formal organizational structure of the regional group. It does not necessarily include all facilities in the region nor every area of hospital service. Any coordinated effort for the operation and improvement of one or more hospital services may be considered as a form of regional coordination.

In a state like Minnesota with relatively few large population centers, a small hospital means a hospital of under 50 beds which may represent the average sized hospital in many states. In Minnesota, outside of the Twin Cities, Duluth and Rochester there are only nine hospitals over 100 beds in size. In considering the question as to how regional coordination can help small hospitals, let us review some of the experiences in various parts of the country.

The Regional Hospital Council of Rochester, New York, carries on a program which encompasses nearly all hospital activities for its cooperating members. Twenty-eight hospitals in eleven adjoining counties participate in the program. Educational and advisory services are provided by the Council with full-time consultants in the fields of accounting, hospital administration, medical records, nursing and purchasing. One of the distinctive features of the Rochester program has been its organizational structure. The legal body is a non-profit corporation composed of representatives of the member hospitals and the public who elect a lay board of directors. Representative physicians from the medical staffs of member hospitals form a group which advises on all professional matters and assumes responsibility for the medical education phase of the Council's program. A like body of hospital administrators advises on the administrative aspects of the program and is responsible for educational activities in hospital administration. This has been a demonstration program,for the past five years, with substantial support from the Commonwealth Fund of New York. In the future it will have to be supported by community resources. However, the group purchasing activities of the Council alone have resulted in substantial, measurable savings to member hospitals. It is interesting to note that the smallest hospital in the group, a rural hospital of only 15 beds, has actively participated in nearly every activity of the Council. Without a doubt, the practicability of regional coordination in many areas of hospital activity has been demonstrated.

Another example of regional coordination is the Bingham Associates Program in Massachusetts and Maine. The Bingham Associates Fund centers its activities around the New England Center Hospital in Boston, the teaching hospital for Tufts College Medical School. Regional hospitals are located in Lewiston and Bangor, Maine and ten to fifteen rural hospitals are grouped around each of these regional centers. The Bingham Associates Fund assists its associate hospitals in obtaining pathological and radiological service, provides funds for postgraduate educa-

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tion of the medical staff and other hospital personnel. It provides consultant services in the fields of laboratory, x-ray, nursing, medical records, dietetics, accounting, purchasing and hospital administration. A regionalized intern-residency program is also conducted by the medical school. The program has established a fourteen-month course in medical laboratory technique which has been quite successful in relieving the shortage of laboratory personnel in the rural hospitals of Maine.

One of the early attempts to coordinate hospital services in rural areas was made by the W. K. Kellogg Foundation in Michigan. The Foundation proceeded on the assumption that the provision of good diagnostic services is the key to improvement of medical and hospital care in the community. The principal need was for specialists to supervise the diagnostic departments in the rural hospitals. Since hospitals of 40 and 50 beds cannot support the services of these specialists full-time, the logical conclusion was for a number of hospitals to combine to use their services jointly. The Foundation made grants for the purchase of equipment to improve facilities in the hospitals and where a group of hospitals agreed to join together, it offered to make up any deficit in operating expenses for a three-year period. This provided the impetus for securing of qualified specialists and technical personnel. Over a ten-year period this program spread to some 42 hospitals throughout the state of Michigan and the joint utilization of radiologists and pathologists in the hospitals of Michigan has become an accepted fact.

A number of joint purchasing programs have been started in addition to the one carried out by the Rochester Council. The programs of the Hospital Councils of Cleveland and Philadelphia have been very successful. The Philadelphia service estimates average savings to member hospitals at seven per cent. Hospitals in southern Michigan have instituted a group purchasing program with the assistance of the Kellogg Foundation.

Several regional programs in medical records have been attempted. The February 1951 Journal of the American Association of Medical Record Librarians relates the experience of programs of this type in three states—Massachusetts, Mississippi, and Texas. In these programs qualified medical record librarians traveling between three to seven small hospitals supervised the work of record clerks who maintained the medical records in each hospital.

Other programs have been organized in the field of postgraduate medical education. Minnesota and Michigan have conducted extensive programs of regional seminars for physicians and postgraduate courses at the teaching centers. Other states have similar programs. New York University Postgraduate Medical School conducts an educational program for the medical staffs of thirteen associated rural and suburban hospitals.

Hospitals in a number of metropolitan areas have found it practical to join together for studies of the hospital needs in their area and better joint utilization of services. State hospital associations in many states have found that organization on a regional basis provides a better means for member hospitals to meet frequently to discuss their common problems. State planning agencies charged with the administration of the Hill-Burton program have delineated regions in their state plans and outlined proposals for regional coordination. Recently the states of Minnesota, North and South Dakota, Iowa and Wisconsin held joint planning conferences to coordinate their planning for hospital facilities along their state borders.

This enumerating of some of the activities toward regional coordination gives a picture of the growing trend toward cooperation for the solution of mutual problems. The experience of those who have tried coordinated programs is encouraging. The greatest benefactors of these regional programs have been the small rural hospitals. At the present time with the complexities of medical treatment and hospital care, only the large hospitals can provide the highly specialized services economically. The small hospital can either provide some of these services at an unusually high cost or do without. By joining together, hospitals have found it possible to provide many of these services at a reasonable cost. It appears to be the best solution to insure the provision of good services in the small rural hospitals.

What can we do to provide regional coordination of services in this part of the country? It is apparent that small rural hospitals cannot support extensive activities in all areas of hospital service. There are, however, problems common to groups of hospitals in various areas which may be met by cooperative effort. In some of the activities the state as a whole may serve as a region. In others, a relatively small geographical area might support a regional activity. Hospitals around a nursing school might cooperate in a nursing program. The purchasing department in one of the larger hospitals

might become the center for group purchasing activities. Hospitals around a center having a radiologist or pathologist might share in the use of their services. Specimens may be sent by mail but the clinical pathologist must be within a reasonable road distance to assist in clinical diagnosis, particularly of tumors, to do frozen sections, perform autopsies, and participate in staff conferences. In all cooperative activities the number of hospitals which may use the service will be limited by their proximity and by the length and frequency of visits necessary to provide optimum service. The objective, of course, is that by regional coordination all hospitals shall have an opportunity to provide maximum service to patients at the lowest possible cost.

Recent events in Minnesota indicate that the trend is in this direction. In the past two years at least eight outlying communities have obtained the service of a resident radiologist and a dozen or more hospitals have begun to receive the services of a visiting radiologist from a nearby center. For several years the State Hospital Association has been conducting regional meetings at which time educational work shops in accounting and medical records have been included. An administrator recently reported that a joint purchasing program for eleven hospitals in Minnesota, North Dakota and Wisconsin was being put into operation.

During the past year a group representing the medical and hospitals associations, the radiological and pathological associations, societies of technologists and x-ray technicians, the University of Minnesota and the Minnesota Department of Health have met to discuss ways to assist in the improvement of diagnostic services throughout the state. The cooperative effort of these varied groups has recently evidenced itself in the joint sponsorship of a regional refresher course in medical laboratory technique which began on April 1, 1952. Eight evening sessions have been held—one each week for eight consecutive weeks. The sessions were conducted at St. Gabriel's Hospital in Little Falls and participants registered for the course from distances as great as 90 miles. On the same evenings physicians and nurses met at St. Gabriel's Hospital for a postgraduate course in obstetrics and maternal and child health. It is expected that similar programs will be extended throughout the state.

These pilot programs have pointed the way and demonstrated the feasibility of regional coordination. It remains for all of us to expand these activities and to weld them into a cohesive program. It would be desirable to have all such activities organized on the same geographical basis but such at this time may not be possible although it may eventually become the pattern. However, we shall be much closer to our objective if we expand the programs now existing in certain areas of the state to all sections of the state and include as many hospital services as possible. If this is done, such regional coordination will be of real benefit to the small hospitals in reaching their goal of providing the ultimate in hospital care for all their patients.

The people of this section of the country rightly assume that they have available, medical and hospital care equal to that found anywhere in the world. If their confidence is to be retained everyone concerned with the provision of medical and hospital services must cooperate in bringing to all they serve the most complete, modern medical and hospital care possible within the geographic and economic limitations of the area. The people must also assume their responsibility to supply the funds to provide the necessary facilities for such activities and to support the services offered.

Measurement of blood coagulation by means of a thromboelastograph is described by Hellmut Hartert, M.D., of the University of Heidelberg, Germany. Time as well as the changes in tension and elasticity of the forming or formed blood clot are recorded. The procedure is based on measurement of the increasing resistance created by the clotting blood, placed between two apposed steel leaflets moving in opposite directions. In 7,500 clotting studies, characteristic patterns were revealed for various hemorrhagic conditions.

Klinische Blutgerinnungs studien mit der Thrombelastographie. Deutsches Arch. f. klin. Med. 199:284-311, 1952.

Tumors of the Small Bowel*

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Prognosis in malignant tumors of the small bowel is almost uniformly poor. As a rule, metastases are already present when the tumor is discovered, a situation which occurs, not because these lesions are rapid in their growth, but because the small bowel, by reason of its fluid content is not distended or obstructed until the growth has become large and well advanced. Symptoms become evident only when some degree of obstruction, hemorrhage, or perforation has begun, and by the time a characteristic chain of symptoms leads to its discovery, it is probable that a tumor has been present and growing for some time.

Recognition of these lesions is difficult and definite diagnosis during life can be done only by roentgenologic studies of the small bowel, or by surgical exploration. The problem, therefore, resolves itself into the proper selection of cases to whom special diagnostic procedures should be applied. This discussion of symptoms and findings leading to earlier diagnosis will be limited to those lesions occurring between the second portion of the duodenum and the ileocecal valve.

All authors are in agreement concerning the low incidence of these tumors. Pridgen and Mayo and Dockerty[1] found only 63 cases of primary adenocarcinoma of the jejunum-ileum in the records of the Mayo Clinic from 1907 to 1947, and Dixon and his associates[2] from the same clinic reported only 49 cases of malignant tumors of the duodenum. Rouse and Reynolds[3] reported two carcinomas of the duodenum and 20 of the jejunum and ileum seen in five Dallas hospitals in ten years. Altemeier[4] stated that in 18 years at the Cincinnati General Hospital, only 20 malignant lesions and 21 carcinoids had been diagnosed. Eckel[5] in 1948 stated that, although a half million patients were admitted to the New York Hospital from 1932 to 1948, the diagnosis of malignant lesions of the jejunum and ileum was established in only 12 cases.

At the Quain and Ramstad Clinic, in the 21 years from 1930 to 1951, only 14 primary malignant lesions of the small bowel and duodenum were diagnosed, comprising three carcinomas of the duodenum, four carcinomas of the proximal jejunum, and four carcinomas of the ileum (one of which was at the ileocecal valve). There was one carcinoid of the terminal ileum, one lymphosarcoma, and one spindle cell sarcoma of the ileum. One benign primary tumor, a leiomyoma of the ileum, was diagnosed during this period. There was also one metastatic melanoma of the ileum.

Small bowel tumors may be found at almost any age, but are most frequently seen in patients in the fourth and fifth decades. Males are affected twice as frequently as females.

Carcinomas of the small intestine are most commonly adenocarcinomas. Some may arise from intestinal polyps. Ewing[6] states that they occur as polypoid outgrowths which finally obstruct the lumen, as tumors which ulcerate early, or as growths which invade muscular and subserous layers to produce early stenosis. In all these cancers, ulceration of the surface is the rule, with some degree of bleeding. Perforation is uncommon and usually results in localized abscess.

Carcinoid tumors are thought to arise from the chromaffin cells in the crypts of Lieberkuhn. Next to the appendix, the ileum is the most frequent location of these tumors. They are usually small, but occasionally may be large, and there may be multiple sites of origin. Carcinoids grow chiefly in the mucous and submucous layers, but invade muscularis and serosa. If ulceration occurs, it is usually shallow, so that melena and anemia are infrequent.[7] As the lesion grows, a chronic progressive intestinal obstruction occurs,

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with recurring attacks of abdominal cramps sometimes related to ingestion of food. Occasionally, the tumor may cause intussusception. These lesions are malignant, since involvement of the nodes is common and spread to the liver not infrequent. The degree of malignancy is low, however, and the prognosis is relatively good.

Lymphosarcoma involves the ileum more frequently than any other portion of the gastrointestinal tract, except the stomach. In general, it tends to occur somewhat more frequently in a younger age group than does carcinoma. The growth may be polypoid[8,9] but is more often an intramural, infiltrating lesion which, in its early stages, may cause intussusception.[10] As it advances, it tends to replace muscularis and submucosa and comes to lie beneath the serosa. In some cases, there is necrosis and ulceration; in others there is gradual dilatation of the gut giving the appearance often described as "garden hose"; or a narrowing of the bowel may occur with stenosis and partial obstruction. Melena is infrequent. There is likely to be rapid progression in the later stages of the disease with cachexia, toxemia, and rapid downhill course.

Sarcoma is very rare in the small bowel and is generally of muscular origin. The type commonly found is spindle cell sarcoma, though leiomyosarcoma or myxosarcoma may occur. The ileum is the most common site. Sarcomas tend to be massive growths, generally of the external type, growing out into the mesentery rather than into the lumen, and thus are less likely than carcinomas to produce obstruction. This may account for the fact that they frequently reach a considerable size before being discovered and are said to often attain the size of a child's head.[11] Early tumors are hard and elastic, but with the central necrosis that occurs as they enlarge they tend to become soft and spongy. The tumors grow slowly and give a better prognosis than carcinomas because metastases occur less freely. The tumor does not tend to recur if excised early.

The true incidence of benign tumors of the small intestine is not known, since most produce no symptoms and are recognized only if demonstrated at autopsy. Adenoma is the type most commonly found and these are most frequent in the lower portion of the intestinal tract. They are usually polyps or papillomas, although the sessile form also occurs. They may be single or multiple.

Myomas are next in frequency. They are of interest chiefly because they are subject to degenerative changes which may result in necrosis and hemorrhage.

Fibromas, mixed tumors, lipomas, and angiomas may also occur.

Aberrant pancreatic rests[12] may also occur and may become large enough to produce symptoms. In the duodenum they are occasionally demonstrated by x-ray and may be confused with polyps or carcinoma.

Primary malignant growths located elsewhere in the body not infrequently metastasize to the small intestine. Tumors of other intra-abdominal organs are the most common primary site, but metastases from skin, breast, testicle, orbit, and cervical glands have also been reported.[11]

Unfortunately, the early symptoms—if there are any—of small bowel tumors, are not recognized as such and are probably indistinguishable from those due to the common transient or functional gastrointestinal diseases.

The first definite symptoms depend largely on the type of lesion. A tumor which ulcerates early is likely to bleed, producing symptoms of anemia; one which projects into the bowel lumen as a polypoid lesion may produce intussusception with its sudden symptoms of obstruction; while a scirrhous carcinoma may cause gradually increasing symptoms of obstruction as the growth infiltrates the bowel wall to produce stenosis.

It is evident therefore, that three main types of symptom complexes may develop: the obstructive syndrome, the bleeding syndrome, or the perforating syndrome.[1] As a late accompaniment of any of these may be added the symptoms due to spread of the growth to a contiguous structure.

The most common presenting symptom is cramp-like abdominal pain. In the unusual case, this may begin with the sudden onset of complete obstruction without previous symptoms and the patient will complain of severe pain, distention, and emesis. More often, however, the trouble begins as a partial obstruction with intermittent attacks of abdominal cramps, with or without nausea or vomiting, and recurring with gradually increasing frequency and severity. The pain is usually referred to the region of the umbilicus and may be aggravated by the ingestion of food, though the relation to the time of the meal may be variable. Co-existence of cholelithiasis or duodenal ulcer may confuse the diagnosis. Mayo and Nettrour[13] reported a case of a patient with jejunal carcinoma in whom a cholecystectomy was done without relief of symptoms, and similarly a patient with duodenal ulcer in whom gastro-enterostomy was done. In neither

case was a jejunal tumor discovered until continued symptoms led to a subsequent operation.

Gas, rumbling, bloating, and the feeling of upper abdominal distress are common symptoms. These may be associated with nausea and anorexia. Abdominal distention, usually associated with the cramp-like pain, may occur, but distention is rare with lesions of the duodenum and upper jejunum and, when present, suggests a lesion of the ileum.

Alteration of the bowel habits is not a prominent symptom as a rule. Mild diarrhea may occur, alternating with constipation or with normal bowel movements.

Patients in whom considerable bleeding from the tumor occurs before obstruction develops may present themselves first with symptoms primarily due to anemia. There is palpitation, dyspnea, or a tight feeling in the chest on exertion, or only weakness, fatigability and listlessness may be complained of. Gross melena may or may not be present, but examination of the stool will show occult blood in a large percentage of cases. A negative test should be repeated if bleeding is suspected, since the bleeding may be intermittent.

These symptoms are produced either by a sudden massive hemorrhage or by long continued bleeding of a lesser degree. The carcinomas tend to ulcerate early and in many cases bleeding occurs in appreciable amounts for some time before symptoms of anemia are evident. All patients with indefinite gastrointestinal symptoms should have the benefit of repeated examinations of the stools for occult blood. There is no other early finding so characteristic of tumor as the presence of blood in the stool, and early detection of gastrointestinal bleeding may make it possible, in many cases, to diagnose these tumors before advanced anemia or obstruction make it obvious that the lesion has advanced so far that a cure is unlikely.

Occasionally, a patient will first present himself with symptoms due to perforation of a growth and the production of definitely localized pain with or without abscess formation. These are, however, usually not the first complaints but merely the culmination of definite warning symptoms previously neglected. Free perforation into the general peritoneal cavity is unusual, a localized abscess being the rule.

In general, all types of tumors of the small bowel produce similar symptoms regardless of the level at which they are situated. However, some exceptions to this rule are of importance.

Tumors of the duodenum produce symptoms suggestive of duodenal ulcer, with attacks of epigastric distress, bloating, and loss of appetite.[2] Pain is often worse with hunger, but with only temporary relief from food. When the tumor invades the common duct or the head of the pancreas, pain may radiate to the back and jaundice is likely to occur. Mistaken diagnosis of primary carcinoma of the head of the pancreas may be made. Bleeding may be a prominent symptom and diagnosis of duodenal ulcer may be entertained. Indeed, ulcer may co-exist, and the diagnosis of tumor may be missed if the roentgenologist, having found an ulcer in the bulb that seems to explain the symptoms is thereby led to neglect careful examination of the remaining duodenum.

In the jejunum, a large percentage of carcinomas occur at or within a few centimeters of the duodeno-jejunal flexure. These lesions result in symptoms of high obstruction, and may produce a high degree of gastric retention suggesting pyloric obstruction. The obstruction may be preceded by symptoms suggesting duodenal ulcer, and the diagnosis may be completely missed if a duodenal ulcer co-exists.

As might be expected, tumors in the ileum produce more typical symptoms of intestinal obstruction with greater distention. There tend to be episodes of abdominal pain, and distention with or without vomiting and occasionally associated with diarrhea, occurring in attacks over several months, increasing in severity until marked obstruction occurs.

The diagnosis of small bowel tumors depends upon the ability of the clinician to suspect the presence of such a lesion. Occasionally, the detection of a movable, firm, abdominal mass may suggest the diagnosis. The presence of occult blood on repeated examination of the stool, with or without associated anemia; a history of intermittent partial intestinal obstruction; or a history of any recurring distress or discomfort that tends to be localized in the region of the umbilicus must raise the suspicion of a tumor of the small bowel and requires systematic roentgenologic study of intestine by repeated serial fluoroscopic and roentgenographic examination.[14] It must be emphasized, however, that x-ray examination of the small bowel is laborious and time consuming, and should not be undertaken until the more common site of disease—the esophagus, stomach, duodenum, and large bowel—are first eliminated as a location of suspected disease.

The roentgenologist can examine the small intestine with a fairly high degree of accuracy. The clinician must keep in mind, however, that

some tumors, because of their small size or their location, may escape detection. In the presence of adequate clinical findings and history, therefore, surgical exploration must occasionally be undertaken in spite of a negative x-ray examination. It will also occasionally occur that careful and expert roentgenologic examination will appear to demonstrate a lesion which does not actually exist. This fact is illustrated by a case we have recently seen. A 75 year old woman presented herself with small bowel symptoms and with a secondary anemia which could not be explained by careful examination of the upper and lower gastro-intestinal tract or by repeated examinations of the blood and bone marrow. Repeated examination of the small bowel by two different roentgenologists, one of whom is nationally known for his work on the x-ray examination of the small bowel, demonstrated a small tumor of the ileum. Exploration failed to discover the lesion. An opportunity for further examination was afforded us when she expired a short time later of coronary occlusion. Autopsy showed the entire gastrointestinal tract to be free of tumor or disease.

In patients in whom small intestinal obstruction is present as demonstrated by clinical examination with or without a flat plate or so called "scout film" of the abdomen, barium studies of the small bowel are unnecessary, and may even be contraindicated. If supportive measures and decompression with a long tube are successful in completely relieving the distention, x-ray examination can be done, if not, operative treatment is mandatory and will make the diagnosis.

TREATMENT

The treatment of choice for all tumors of the small bowel is primary resection of an adequate segment of the involved intestine together with its mesentery, whenever possible. When the lesion is considered too far advanced for resection, a palliative short-circuiting operation should be done if practicable. This is particularly true in patients with lymphosarcoma, since once the obstructive symptoms are relieved, long periods of remission can often be obtained with roentgen therapy.

SUMMARY

1. The most important single factor in the diagnosis of tumors of the small intestines is the ability of the physician to suspect their presence.

2. Diagnosis of tumor of the small bowel should be entertained whenever persistent gastrointestinal symptoms cannot be otherwise explained.

3. Occult bleeding occurs early in the course of small bowel carcinomas and its detection is important if early diagnosis is to be made.

4. Roentgenologic study of the small bowel should be done: a) in patients with small abdominal masses; b) in patients with persistent or intermittent abdominal pain, persistent vomiting, melena, or diarrhea, not explained by routine examination of the gastrointestinal tract, gallbaldder, and the kidneys.

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MEDICAL VOCATIONS

In this department, from time to time, THE JOURNAL-LANCET *will present a series of articles on the vocations and professions which are closely integrated with the practice of medicine. It is hoped in this way to give the physician a broader knowledge of the training required, the general scope of duties, and the problems faced in the work of his professional associates.*

The Medical Social Worker

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MEDICAL SOCIAL WORK is one of the younger of the professions which have entered the hospital. In 1905, Dr. Richard Cabot, in his practice in the clinics of the Massachusetts General Hospital, became discouraged because some patients, with minor illnesses, never seemed to recover and kept returning for care. His clinic nurse, sent to visit the homes, found that patients were unable to carry out the doctor's recommendations. Some did not know what was expected, others did not have the money to do what the doctor suggested, some had personal problems which prevented them from doing what was necessary. An infant patient Dr. Cabot was most concerned about continued to have respiratory infections because it lived in a cold damp tenement basement. Miss Pelton, the nurse, found many charitable organizations in Boston where assistance could be obtained but the patients did not know where to go for what they needed. Dr. Cabot decided there should be someone in the clinics to take care of these problems. The nurse soon discovered she could help many because she was a part of the clinics and knew about medical conditions.

From this beginning, medical social service departments have been established in many hospitals and clinics throughout the world. The number of available workers has never been sufficient to supply the expansions in the program, and as a result, there has been a tendency for departments to be established in the larger hospitals. The professional course in medical social work requires two years of graduate training including 400 hours of supervised experience in a department.

The social service department of a hospital is concerned with patients who have problems which interfere with their medical care or with their ability to carry on in life. Problems may be concerned with the patient's feelings about his illness, his social situation, or his environment. Some patients, incapacitated by illness, are no longer able to care for themselves when they leave the hospital and must plan a whole new way of life. Frequently they require a place to live where they can be cared for, or financial aid to provide for themselves or their families. They need to be trained in a new occupation so that they will be able to work, support themselves and their families, and be contributing members of the community. Young mothers, suffering from heart disease or the residual effects of polio, need help in securing someone to care for their small children. Patients may need aid in completing medical care, because their condition may necessitate the use of specialized hospitals such as a state mental institution or a tuberculosis sanitarium. In the hospital there are patients who become bewildered by illness and by medical procedures. There are relatives who, because they do not understand the medical condition, make it difficult for the patient to accept what the doctor tells him to do. Patients away from home and unable to do things for them-

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selves become anxious when faced with personal and family difficulties. There are times when patients with serious personal or social conditions which cannot be changed need help in understanding the situations and in accepting them as they are.

The purpose of social casework is to assist those who are able, with some help, to work out a satisfactory solution to their own problems. Through interviews with the patient, the social worker helps him to identify his problems and to understand some of the reasons behind them. A knowledge of human behavior is necessary in determining how best to work with the patient. The worker must decide whether a patient, if he had better self-understanding, would be able to work out a satisfactory solution or whether anxieties and strains are so great that he should accept the practical aids available, or whether, perhaps, a combination of both types of service are indicated. There are some who need to keep their problems, for to dislodge them would require giving up defenses useful to adjustment. Sometimes the social worker finds serious personality disturbances requiring the attention of a psychiatrist. The worker gives services which meet practical needs, and does those things required to modify the environment and relieve the patient's stresses and strains.

The social worker in a hospital or clinic facilitates the medical care given the patient by the social casework she performs. It is essential in working out the problems referred to her, that she determine whether she can give the service herself or whether it could best be provided by some community agency. Many patients, when given proper information as to where they can get help, are able to go on their way. Others, because of personal problems, are blocked in doing what is essential to their medical treatment. For example, some have great conflict about taking financial support from the public funds and cannot make an application until they understand why they feel the way they do about accepting help. An unmarried mother needs to work through her attitude about her child before she can decide to keep her baby or give it up for adoption. There are relatives who reject their parents when they are ill and hospitalized and resist making plans for them while others make sacrifices to the detriment of their own small children. All of these need social casework so that the best plan can be effected.

There are those patients who need someone with whom to talk over their problems in order to get a better perspective. Since the social worker is not directly involved in medical treatment, she is often in a strategic position to be of service to the doctor. Patients who have fears about illness, anxieties about family situation or concerns about the future all can benefit from a discussion with a social worker. Since she is familiar with their medical and social situation and knows what practical assistance can be secured, she is able to help.

When the service decides that the patient's needs can best be provided by a local agency, the social worker requests assistance from that agency. Since she is familiar with available resources, she knows where to solicit the assistance or financial aid. In this day of highly complex organizations, locating of resources for specific purposes is almost a technical function. Every community, regardless of size or location, has public and private organizations and agencies, as well as clubs, societies, and private endowments that give service or financial support to people who have special requirements. Public agencies are legally responsible for the support of the destitute and for medical care of the residents of their jurisdiction. However, since medical care is complex and requires many services and supplies, it is frequently impossible to obtain all that a patient's condition demands from these agencies, and supplemental aid must be located.

Patients are helped to secure the financial assistance required or the casework services indicated from agencies and organizations in the local community. For example, a diabetic cannot control his condition without following a diet. If he is receiving a public assistance grant, his food allowanee must be increased. This is done by referring recommendation to the welfare board or the relief department, and additional funds are granted. A patient who has had a leg amputation, even though fully recovered, cannot return to work until provided with an artificial appliance. Frequently, county welfare bords are unwilling to pay for a prosthesis and it is necessary to locate some other agency, club, or organization willing to provide the money. If patients cannot accept or understand the seriousness of their condition and are negligent in continuing medical care, it is necessary that the relatives or county nurse is informed so that supervision can be given. During hospitalization of children, doctors may be suspicious of serious child neglect. It is essential that the county welfare worker or the public health nurse be advised of the situation so that they can observe the child, from time to time, to make certain that it

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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.*

Clinicopathological Conference

Minneapolis Veterans Hospital*

Edited by JAMES F. HAMMARSTEN, M.D.
Assisted by ROBERT I. LUBIN, M.D. AND DONALD FRY, M.D.

PRESENTATION OF CASE

First admission (September 13, 1947): A 44 year old gas station attendant was admitted because of weakness of the left leg, numbness of the left arm, and dizziness. All symptoms began suddenly on August 26, 1947. He had improved by the time he was hospitalized.

He had jaundice in 1935 and 1945.

Physical examination was negative except for neurological findings. There were absent left abdominal reflexes, hyperactive knee and ankle jerks on the left, unsustained left ankle clonus, and incoordination and weakness of the left leg.

The temperature and pulse were normal. The blood pressure was 130 mm. Hg systolic and 80 diastolic.

All studies were normal including the following: routine hemogram, urinalysis, erythrocyte sedimentation rate, blood Kahn, spinal fluid, x-ray films of the chest and skull, and air encephalograms.

The strength in the left leg improved, but the other neurological abnormalities remained.

Second admission (January 18, 1949): On January 1, 1949 he developed a right hemiplegia. By January 11 he could move his right arm and leg. Improvement continued until admission.

Physical examination was similar to that on the previous hospitalization. In addition there was weakness of the right arm and leg, increased reflexes on the right, bilateral positive great toe signs, and bilateral unsustained ankle clonus.

Laboratory studies were again normal. He gradually improved and was discharged after a few weeks.

Final admission (March 31, 1951): He remained asymptomatic until February 1951 when he began to have nausea and vomiting. These episodes apparently were precipitated by fatty foods. He also had anorexia and weight loss. For 3 weeks prior to admission he had chills and fever and a nonproductive cough. He noted extreme weakness and fatigue for two weeks. For two weeks he also had nocturia, dysuria, urinary frequency, and polydipsia. On the day of admission he had diarrhea. He was transferred from another hospital where he had been for ten days.

Physical examination showed a chronically ill, well-developed, poorly nourished, dehydrated man. The liver and spleen were palpable two finger breadths below the costal margin. There were bilateral axillary nodes measuring 1 to 1½ cm. in diameter. The only residual neurological abnormality was a hyperactive left knee jerk.

The temperature was 99° F., the pulse rate 102 per minute, and the blood pressure 92 mm. Hg systolic and 68 diastolic.

The hemoglobin was 12.9 gm. per 100 ml., and the white blood cell count 11,200 per $mm.^3$ with 53 per cent neutrophils, 40 per cent lymphocytes, 3 per cent monocytes, and 4 per cent eosinophils. The erythrocyte sedimentation rate was 32 mm. in 1 hour. The blood Kahn was negative. The urine was normal except for an occasional hyaline cast.

The heterophil antibody titer was negative. The bromsulfalein retention was 14.2 per cent in 45 minutes, the cephalin flocculation 0 in 24 and 48 hours, the 1 minute serum bilirubin 0.2 mg. per 100 ml. and the total 1.0 mg., the thymol turbidity 1.7 units, the zinc sulfate turbidity 12.5 units, and the 2 hour urine urobilinogen 1.0 Ehrlich unit. The stools were negative for occult blood, ova and parasites.

The blood urea nitrogen was 12.5 mg. per 100 ml., the CO_2 14.4 mEq. per liter, the serum chloride 80.4 mEq. per liter and the serum potassium 5.32 mEq. per liter. On April 3 he became disoriented, stuporous, and then unconscious. He still appeared dehydrated and had frequent loose stools. His blood pressure was 90 mm. Hg systolic and 60 diastolic, but his temperature rose to 103.6° F. (rectally). The spinal fluid was normal and a blood culture nega-

*Published with approval of Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

tive. Intravenous saline and glucose, and antibiotics were given. On April 4 the blood chemistry studies were repeated with the same findings as on admission. The serum sodium was 111.3 mEq. per liter and a non-fasting blood glucose 102 mg. per 100 ml.

The hemoglobin was 10.2 gm. per 100 ml. His blood pressure remained the same. He became somewhat responsive but still was disoriented. On April 6 the serum chloride had increased to 100.9 mEq. per liter and the sodium to 123 mEq. per liter. The potassium was 4.8 mEq. per liter. The CO_2 and blood urea nitrogen were unchanged. His urine output was between 1 and 1.8 liters daily. He remained febrile and died on the morning of April 6, 1951.

DISCUSSION

DR. EDMUND B. FLINK*: It is difficult to make a neurological diagnosis on the first two admissions. He had no localizing evidences of a space-occupying lesion. The relatively mild nature of these hemiplegias suggests that a small area was affected by a thrombus. Hypoglycemia can produce transient hemiplegia but the neurological signs persist only a day or so. Hemiplegia on the basis of a disseminated demyelinating disease is possible but there is no corroboratory neurological evidence. I favor a diagnosis of bilateral small cerebral thrombosis.

All of the symptoms during the final episode can be explained on the basis of adrenal insufficiency with the exception of polydipsia and the urinary tract symptoms. The urine volume is usually normal in adrenal insufficiency. The polydipsia may be related to the patient's fever. I cannot explain the dysuria and nocturia with a normal urine.

The hypotension fits very well with adrenal insufficiency but any dehydrating disease may cause hypotension of this degree. The absence of pigmentation does not deter me from making a diagnosis of acute adrenal insufficiency.

The absence of a neutrophilic leukocytosis in the face of a severe illness is a fairly strong peg for me to lean on. There are many diseases which will produce a leukocyte picture like this. In typhoid fever the total leukocyte count is usually lower. A gram negative bacteremia produces more profound collapse and there is usually a neutrophilic leukocytosis.

Splenomegaly and lymphadenopathy suggest Hodgkin's disease. Lymphadenopathy, however, may occur with adrenal insufficiency. I am unable to account for the splenomegaly on the basis of adrenal insufficiency.

The bromsulfalein test is abnormal. In 5 of 8 patients with Addison's disease studied at the Peter Bent Brigham Hospital an abnormal bromsulfalein test was found. The preceding jaundice suggests the possibility of cirrhosis; however, other than the bromsulfalein the other liver function tests are normal.

The low CO_2 combining power, low chlorides, and low sodium favor my diagnosis. It is a little unusual to get a CO_2 as low as this in Addison's disease, but it is not impossible. The normal blood urea nitrogen is very unlike Addison's disease. A serum potassium of 5.3 is not as high as I would like.

What are the other conditions that can produce an electrolyte disturbance of this nature? Vomiting can lower the chlorides to this extent. Diarrhea can also do this, but I gather from the protocol that the diarrhea was not severe. Renal disturbance can produce electrolyte changes of this degree. If he had a specific tubular abnormality, it would be possible to get a change like this. Most instances of tubular disturbance have a high chloride. He has no real evidence for renal dysfunction. Cirrhosis of the liver can cause electrolyte disturbance of this severity under very special circumstances. When repeated paracenteses have been done and the patient is on a salt-restricted diet, electrolytes at this level can develop. Another disease that produces lowering of the sodium chloride and CO_2 is severe tuberculosis, either pulmonary or non-pulmonary. A cerebrovascular accident can also produce these changes. However, the sodium is usually not lowered to this

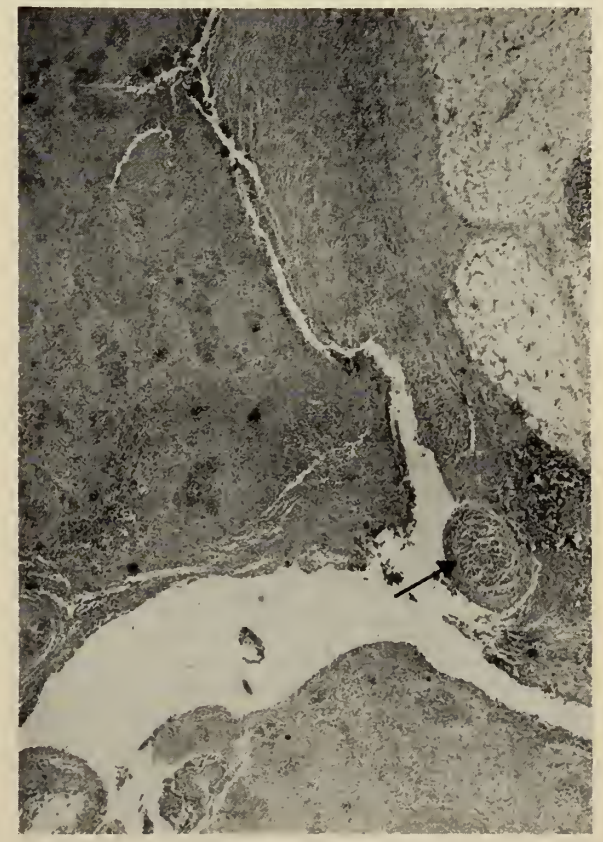

Fig. 1. Photomicrograph of the adrenal gland. The gland is almost entirely replaced by tuberculous tissue. The arrow points to a small island of adrenal cortex.

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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.*

Some Physiological and Clinical Aspects of 24-Hour Periodicity*

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DEFINITIONS

One of the difficulties "in correlating the various views and opinions on how periodic biological phenomena are established and maintained lies in the confusion of terms used".[1] The words periodicity, cycle, rhythm, fluctuation, oscillation, variation, swing, tide and pendullation are among the terms used by various authors to describe regular repetitive changes in biological variables. Efforts to systematize these "synonyms" are as numerous as are the disagreements resulting from such endeavors. Their review lies beyond the scope of this paper. It appears necessary, however, to present certain definitions before introducing the subject.

The term "periodicity" will be used to denote all regularly repetitive changes occurring either in animate or in inanimate nature, regardless of either the time period involved or the mechanism instrumental in the appearance of periodic changes. The term "cycle" will be employed to denote the whole of certain specified changes recurring within an organism in an integrated fashion, resulting from a defined mechanism and having a recognizable time-period. This definition is in keeping with the use of this word in the well-established terms "cardiac cycle" and "estrous cycle."

The term "rhythm" will denote either the regularly repetitive quantitative changes which give rise to a cycle or the measurable manifestations of such processes. This definition of "rhythm" should forestall the inference that physiological rhythms are *mere* reflections of time associated environmental changes.

The term "phase" will be employed for specified parts of a rhythm. The reference point for the beginning of the ascending phase of a rhythm will be the minimum in the respective quantitative variable. Conversely, a descending phase of a rhythm will begin at the time point when the maximum value is obtained for the variable measured.

To denote the time of day noon will be designated as 12:00, midnight as 24:00 and other times of day correspondingly.

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The admittedly cumbersome adjective "24-hour" will be employed to denote periodicities with a unit of time of 24 hours.† It is to be noted that "diurnal" will therefore designate the day-time and not the entire 24-hour period (although it has been used with this later denotation in earlier publications of this author as well as in the publications of many other authors). This restriction in the meaning of "diurnal" is made in view of the established uses of this term for distinguishing either seizures or activity limited mainly to daytime from those limited to other parts of the 24-hour period.

THE PRESENT STATUS OF KNOWLEDGE ON PHYSIOLOGICAL 24-HOUR PERIODICITY

Current interest in biological periodicity is illustrated by the table of contents of a recent issue of Pflueger's Archiv.[6] Five of the six articles deal with aspects of periodicity in physiological systems. In an issue of Studium Generale, eight out of a total of thirteen articles are concerned with analyses of the significance of the concepts of periodicity and rhythm in the different fields of science.[7] An International Society for the Study of Biological Rhythms, founded at Ronneby, Sweden, in August, 1937, held its third meeting in 1949 in Hamburg, Germany, and plans another meeting in 1953.[8] It aims to coordinate efforts in the study of problems of biological periodicity. Papers presented at the meetings of this society are published, some of them in full, others as abstracts.[9–11]

Seventy titles of articles published on biological periodicity in 1949 are listed by Vering.[12] He aims at demonstrating the growing interest in the field by listing the titles of publications in a chronological sequence, starting with 1875. More extensive source material (through 1948) on the subject of biological

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†The term "diel"-rhythm proposed by Carpenter for 24-hour rhythms in 1932,[2] 1935,[3] and 1938[4] and accepted by Calhoun in 1944 and in 1945[5] has not yet come into general use.

periodicity in general and especially on 24-hour periodicity is available in a considerable number of review articles, discussed by Kleitman in a "Review of Reviews."[1] A review by Menzel in 1952[13] cites a considerable number of recent publications. It is evident from these reviews that the field of 24-hour periodicity has been a subject of extensive investigation. The ubiquity of phenomena with 24-hour periodicity is further apparent. The literature on this subject seems to be more extensive than the literature on other biological periodicities, but up to the present the great quantity of publication concerning 24-hour rhythms has resulted in relatively slight contributions to basic and clinical medicine. Certain other cycles, having a unit of time longer or shorter than 24 hours, are among the cherished bases of medical science. The cardiac and the estrous cycle are cited as examples of periodicity which have been admitted to the body of physiological knowledge. Their importance to clinical medicine needs no emphasis. An understanding of them is a prerequisite for the practitioner and for the basic scientist. They are essentials of the medical curriculum. At the same time textbooks devote a few paragraphs to temperature rhythms; other repeatedly described 24-hour periodicities are of interest mainly as a source of variability in experimental data. More than one medical writer exhibits the attitude which has allowed "coincidental" to be used as exact synonym for "physiological" with respect to 24-hour periodicity.*

There is general agreement that this situation will last as long as "the part played by the organism" in the maintenance of 24-hour periodicity "remains unexplained.[1,15–17]. What is needed is the recognition that "an exceptionally substantial and durable self-winding and self-regulating physiological clock[15] within the organism is responsible for 24-hour periodicity, just as we already recognize the role of the pace-maker in the cardiac cycle and the role of the ovaries in the estrous cycle. It is in a spirit of hopefulness that this mechanism can eventually be localized that a student of physiology accepts this opportunity to discuss certain aspects of 24-hour periodicity. The phenomena discussed are selected from different levels of integration of the mammalian organism. They are presented as illustrative examples of the field, and thus, perhaps, of the significance of the mechanism involved. The role of adrenal secretions in the maintenance of 24-hour periodicity in man will be suggested.

ILLUSTRATIVE EXAMPLES

1. Epilepsy

The distribution of seizures during a 24-hour period is definitely not random in many of the patients in a population of epileptics. It may be of more than local interest to note that a method of recording the time of day when seizures occur was in practice at Faribault, Minnesota, as early as 1883, when Dr. C. A. Rogers assumed charge of that institution.[18] It appears that among the various "periodicities" noted in patients with convulsive disorder† the recurrence of most seizures at a given time of day has especially impressed clinicians. Many epileptics are able to state with remarkable accuracy the hours of the day when most of their seizures occur. Once established, such a regularity in the appearance of seizures became a challenge for investigators, anxious to use this phenomenon as a clue to the problem of seizure mechanisms. Their efforts have yielded data which confirm the earlier clinical impression and demonstrate 24-hour periodicity in the occurrence of epileptic seizures.

Féré, in 1888, is apparently the first to plot along a time scale of 24 hours the numbers of seizures noted in a group of epileptics during 60-minute periods. He is also apparently the first to report marked differences in numbers of seizures due to the time of day.[20]

Gowers, in 1901, states that it is rare for attacks to occur during the first half of the night and that although they may occur as the patient is going to sleep, this is very uncommon, when compared with the frequency of seizures during the process of awakening.[21] Langdon-Down and Brain, recording the time of occurrence of 2524 seizures in 65 patients, confirm the peak in numbers of seizures reported for the morning hours by Gowers: most seizures are observed between 03:00 and 08:00.[22] The unequal distribution of seizures during the 24-hour period in certain patients is the basis for several classifications of epileptics. It can be seen from table I that a diurnal and a nocturnal type of epileptic, named after the time of day when most of their seizures occur, are first distinguished from the diffused type, with a random distribution of seizures. A tendency for both the diurnal and the nocturnal type to be converted into the diffused type, during the continuance of the disease is also noted.

TABLE I

Classifications of Epileptics According to Time of Day When Most Seizures Occur

Figures represent number of patients of a certain type, expressed as per cent of cases examined.

Section I. Breakdown into types by independent authors

Type	Authors*			
	(21)	(22)	(23)	(28)
Diurnal	45	42.5	45.2	37.5
Nocturnal	22	24.2	19.3	38.5
Diffused	33	33.3	35.5	13.5
Awakening	—	—	—	10.5

Section II. Conversion of types during continuance of disease (22)

Type	Duration of Disease		
	10 years	10 to 20 years	20 years
Diurnal	47	40	36
Nocturnal	28	20	21.5
Diffused	25	40	42.5

*Numbers in parentheses refer to bibliography.

Patry, in 1931, reports on the time distribution of 1013 seizures in 31 adult epileptics.[23] He accepts

*One reads in 1951 about "Physiological *or* Coincidental" changes which recur every 24 hours.[14] (Italics mine.)

†Periodicity in the course of an attack,[19] the apparent relationship of seizures to the season of the year, to the monthly period.

the classification suggested earlier and finds that in a nocturnal group 84 per cent of the seizures occur between 20:00 and 08:00, while most seizures in a diurnal group occur between 04:00 and 16:00. A decline in periodicity in the occurrence of seizures with prolonged continuance of the disease is again noted.

The findings of Hopkins[29] agree with those of the authors mentioned above. Furthermore, she notes that younger patients have most of their seizures over a smaller fraction of the 24-hour period than do older patients; in the former a peak incidence of seizures is reported at 05:00, while two peaks are noted at 02:00 and at 07:00 in patients over 15 years of age. As in the records published earlier, the highest incidence of seizures in all the patients studied by this author falls between midnight and 08:00.

A breakdown of the hourly incidence of seizures in patients with convulsive disorder leads Magnussen to define several additional types of epileptics, according to the time of day when their seizures occur.[25] Among other types, he adds an "awakening type" to the diurnal and nocturnal types described earlier.

Magnussen conceived the valid plan of employing 24-hour studies for an experiemental approach to the problem of seizure mechanisms. But his attempt to detect a relationship between variations in blood sugar level and the time of occurrence of seizures yields negative results, in keeping with the data obtained by Lennox.[26] Likewise negative is the outcome of studies on variations in brain volume, in cerebral spinal fluid pressure and in hematocrit levels. It is only the relationship to sleep which appears to be established clinically by all the authors concerned with the problem of 24-hour periodicity in the occurrence of seizures.[20–28]

The time distribution of 39,929 epileptic seizures is discussed by Griffiths and Fox in 1938.[28] Only 14 out of a total of 104 cases are classified as "diffused," a relatively small number, when compared with the percentage figures given by earlier investigators (see table I). The remainder of their cases includes 40 "night fitters," 39 "day fitters" and 11 "rising fitters." These authors discern a triple wave in number of seizures, with a main peak from 06:00 to 07:00 and with lesser peaks from 11:00 to 12:00 and from 22:00 to 23:00. Maxima in seizures are thus noted in this as well as in earlier reports at the times of onset and of termination of sleep. The "rising fitters" appeared to be a particularly intelligent group, in contrast to the "afternoon fitters," a group of deteriorating or low-grade cases.

Another clinical impression of these authors concerns a change in the periodicity of seizures induced by drugs. Scattering of seizures due to anticonvulsant medication is found to be more common than peaking.* Griffiths and Fox make the assumption that all seizures occurring in series are parts of the same epileptic manifestation, which started with the first seizure. The time peak of seizures is therefore determined by noting only the times of occurrences of the first in a series of seizures. This difference in procedure may contribute to the difference in the figures given for the frequency of certain types of epilepsy, by various authors. This is apparent from a comparison in table I of authors 21, 22 and 23 with author 28. Griffiths and Fox point out that the determination of peak hours in seizures is of more than academic interest; that "biochemical investigations made soon after a seizure are likely to be of little value because they may be mere expressions of metabolic processes occurring in the fit itself." Cases with clear-cut time peaks are therefore recommended as subjects for research purposes. It is believed that serial estimations covering full 24-hour periods will show what alterations occur in relation to the time peak.

In view of the foregoing discussion it appears proper to conclude that a 24-hour periodicity in the occurrence of seizures in certain epileptics has been found by all those investigators who have analyzed their data for the presence of this phenomenon. Yet the status of knowledge on this clinical aspect of 24-hour periodicity is in a purely descriptive stage. Advances in the field must await the detection of the physiological mechanism which determines a 24-hour spacing and furthermore correlates this 24-hour periodicity with the alternation of sleep and wakefulness, or perhaps rather with the alternation of rest and activity.

II. Mitosis

A 24-hour periodicity of mitotic activity in laboratory animals and in man will be discussed next as an example of a biological rhythm in a fundamental cell mechanism. This periodicity is evidently physiological, even though the abundant data on which the observation of periodicity can be based have been recorded by workers in morphology and pathology who, with a few notable exceptions, have not sought to identify the physiological mechanisms of the phenomena they were investigating.

After the earlier demonstration of 24-hour periodicity in mitotic activity of plants,[29,30] Fortuyn van Leyden (1917) was apparently the first to present evidence of periodicity in the mitotic activity of mammalian tissue.[31] This author noted that the number of mitoses in the mesentery, in the corneal epithelium and in the crypts of Lieberkuehn of two-day-old kittens increased in the evening and early morning and declined in the late morning and in the early afternoon. In 1924 she found for the materials from her first study that the same pattern of activity held in the spleen, lymph nodes, thymus and bone marrow.[32] Another publication of this author in 1926 reported that the mitotic rate in the crypts of Lieberkuehn in two-week- old mice was maximal

*It is noted that on the basis of less extensive material, Langdon-Down and Brain had stated that medication did not appear to influence the time distribution of seizures.[21]

in the late morning and steadily decreased to reach a minimum in mid-afternoon.[33]

Several years later, Ortiz Picon investigated the effects of aging on the mitotic rate in the epidermis of mice.[34] He noted a decrease in the number of mitoses during the evening and early night hours to about one-third of the noon value, and found this decrease to be more significant than the decrease in the average number of mitoses with age. Picon's very limited data, obtained however on littermate animals of the same sex, fed the same diet and kept under comparable conditions, are summarized under the heading "Something about time of day and cell division" and are "meant to demonstrate the existence of an influence of the time of day upon cell division in the epidermis solely in order to forestall possible mistakes in interpretation of data regarding mitotic rates at different chronological ages."

This conclusion illustrates the attitudes toward phenomena with 24-hour periodicity exhibited by investigators, who regard 24-hour periodicity merely as a source of variability in experimental data. In fairness to Ortiz Picon, however, it should be mentioned that this author alludes to the possibility that periodically secreted hormones could bring about a periodicity in mitoses. He thus hints at the broader significance of the phenomenon.

A year later, Carleton reports a maximum around midnight and a minimum around noon for the numbers of epidermal mitoses in 8 to 168 hour-old male mice, kept under routine circumstances of illumination.[35] In the course of the same investigation, she found (a) a periodicity in mitotic activity of mice kept in darkness from the 23rd to the 37th day post partum, and (b) a loss of periodicity in the mitotic activity of a small series of immature animals, exposed continuously to artificial light.

A thorough demonstration of periodic activity in the epidermis of the albino rat is given by Blumenfeld,[36] who also points out that evaluation and/or comparison of data obtained in investigations on periodicity is feasible only under controlled circumstances. He is apparently the first investigator who endeavors to control the age, the species and the number of animals in a sample as well as the external conditions of the experiment.[37] In skin from one month old rats, kept under normal conditions of illumination, he found four times as many mitoses at 08:00 as at 20:00. This author suggests that the factors which regulate mitosis vary inversely with the function of an organ. Mitotic activity in the renal cortex is found to be minimal at the time of maximal urinary excretion and maximal at the time of minimal urinary excretion.[38] A similar inverse relationship is found between the rate of mitotic activity in the submaxillary gland and that of functional activity, which is associated with food intake.[39] The basic processes of a cell are divided by this author into functional and vegetative activities. One state ceases when the other begins. Cells undergo division during the vegetative state, upon cessation of the functional state. This concept has been formulated earlier by Politzer,[40] who found that moving cells do not divide and by Peter,[41] who found that increased activity in the tubular epithelium of the renal cortex inhibits mitosis and that decreased activity stimulates it.

Blumenfeld concluded that the mechanism of periodicity in mitotic division must reside within an organ itself. But later work has demonstrated for several tissues a relationship between the periodicity in mitotic division and the periodicity in the activity of an organism as a whole.[42–44] This observation suggests a mechanism of integration of 24-hour periodicities, including mitotic periodicity, at the organismic level, rather than at the organ level exclusively. Bullough determined the 24-hour rhythm in spontaneous bodily activity of 3 to 4 month old male mice simultaneously with the 24-hour rhythm in mitosis of the skin and various other organs. He noted a 24-hour periodicity in the average number of mitoses in the epidermis, the esophageal and duodenal mucosa, and the epididymis, which showed an inverse relationship to bodily activity. A minimum in mitotic activity was found during the waking hours and a maximum during resting. The fall in mitotic rate, which was observed in controls subsequent to the evening increase in bodily activity was delayed when, by means of a hypnotic, some animals were induced to sleep beyond this time. Conversely, by forced exercise, mitotic activity was kept at a low level. Furthermore, it was noted in this latter study that the mitotic rate in animals forced to exercise fell below any previously noted minimum, and remained depressed after the animals had been removed from the activity cage and allowed to nap for 2½ hours. "The outcome of the revolving box experiments seems to indicate that excessive exercise or a heightened metabolic rate results either in the production of a mitosis depressing substance which takes some hours to be eliminated, or in the using up of some mitosis stimulating substance which takes some hours to reform in sufficient quantity."

Further studies by Bullough[45] revealed an inverse relationship between the 24-hour periodicity in blood sugar, described for the rat earlier by Pitts,[46] and the periodicity of mitotic activity. During sleep the blood sugar decreased while the mitotic rate was increasing.

Cooper[47] is apparently the first to demonstrate periodicity in mitotic activity of human epidermis. She examined the prepuces of 57 neonates and noted an increase in the average number of mitoses in the late afternoon and early evening, with a subsequent decrease in the later part of the night, which ends in a lower average number of mitoses in the morning. Plotting mitosis against time of day, there is a suggestion of minor maxima and minima within the 24-hour periodicity, indicative perhaps of several alternations of the rhythm during a 24-hour period. Studies on a smaller number of prepuces by Broders and Dublin,[48] in the same year, confirm Cooper's results.

The absence of 24-hour periodicity in mitotic activity of a malignant tissue was demonstrated by Dublin, Gregg, and Broders in specimens from five carcinomas of the large bowel.[49] This finding was extended by the experiments of Blumenfeld to induced epidermoid carcinoma in the epidermis of male mice.[50] The cells of the tumor were found to divide at a uniformly high rate: the mitotic activity of the malignant tissue was comparable to that seen in the epidermis of non-tumorous controls when the rhythm of the latter was at its peak. This finding gains in significance from the demonstration of the same author that in contrast to malignant tissue, the regenerating epithelium of the rabbit had a higher mitotic rate than the rate of controls, yet still exhibited periodicity.[51] It is thus apparent that in a first descriptive stage of our knowledge on mitosis, a 24-hour periodicity in the average number of mitoses has been ascertained for a variety of tissues, in different species and at different chronological ages. The 24-hour periodicity has been reported to be synchronized with the activity, as well as with the feeding habits[52] of the animal. It has been reported to persist for at least two days in a "constant" environment, and it is modified under various experimental circumstances. It is different at different chronological ages. It is seen in rapidly growing epithelium,[51] yet absent in malignant tissue.[49,50]

The data reviewed are compatible with the assumption of a physiological 24-hour rhythm in mitotic activity, which is obliterated under certain pathological circumstances. As in most other fields of biological 24-hour periodicity, the factors with which the rhythm is synchronized, rather than the mechanism which brings about the rhythm, have been subjected to extensive investigation. It appears reasonable to assume that a 24-hour periodicity in mitoses of plants, which are dependent upon periodic stimulation by light, is *due to* light (or: has light as its mechanism), if upon cessation of periodicity in illumination the periodicity of mitoses is found to be obliterated. This conclusion can hardly be applied to those animals which manifest periodicity in mitoses under the circumstances of "constant darkness." Furthermore, it would be unjustifiable post hoc propter hoc reasoning to assume either (a) that a 24-hour rhythm in mitoses of higher mammals is *due to* periodicity in feeding, in activity or in environmental temperature, or (b) that this rhythm is a *direct* function of periodic changes in blood glucose or liver glycogen contents.

For the purposes of this discussion the whole of 24-hour rhythms, including a rhythm in mitotic activity, will be conceived as a series of physiological processes, integrated into a physiological sequence by a physiological mechanism. Until proof is offered to the contrary, the same physiological mechanism which brings about a 24-hour cycle by integration will be assumed to adapt this cycle to the environment, by its synchronization with periodic environmental stimuli. It is this mechanism which is as yet unexplained and thus constitutes a challenge for the physiologist. Investigations on this mechanism could yield information pertaining to some of the as yet unanswered questions about the effects of growth hormone. In addition to a better understanding of the complex factors governing growth, a study of the changing rates in mitosis could be of considerable value for the understanding of neoplastic processes. To achieve such a goal, reorientation of research from the study of environmental factors to the investigation of the mechanism mediating effects of environmental factors appears desirable.

III. The 24-hour Eosinophil Rhythm

Many factors contribute to the variability in number of eosinophils, and this fact has made it difficult to establish the occurrence of 24-hour periodicity in this variable and to recognize its significance. A further obstacle which is usually cited in connection with the problem is the error associated with the technique of counting. But the insufficient standardization of circumstances of observation, the heterogeneity of the populations investigated, and the use of a small sample size appear to be sources of error at least comparable in magnitude. It should also be recognized that the phenomenon discussed appears with predictable certainty only as a group phenomenon. Data on *absolute* counts (expressed as cells per cu. mm.) over 24-hour periods, even though obtained with the best counting chamber methods now available, may require the application of involved statistical procedures in order to display the significance of an "hour of day" effect, that is of 24-hour periodicity. Moreover, an analysis of variance based on absolute eosinophil counts may not suffice to display the character of the eosinophil rhythm, unless effects like those of differences (a) among subjects and (b) among days of investigation are eliminated.

The conversion of absolute eosinophil counts into *relative* eosinophil levels by expressing each count as per cent of the 24-hour mean can then be undertaken to eliminate sources of variation other than the "hour of day" effect. It can be seen from table II that a highly significant endogenous eosinopenia may thus be demonstrated beyond question by employing relative eosinophil levels, rather than absolute counts for the analysis of variance. The "hour of day" effect ("hours" in table II) then stands out with unmasked clarity, being highly sig-

TABLE II

Analysis of variance summary for relative eosinophil counts from institutionalized subjects studied during the morning hours (05:00, 06:30, 08:00 and 09:30) on several days of investigation

Group	Source of variation	D.F.	Variance	F
I (Males)	Subjects	7	0.184†	0
	Days	2	0.045†	0
	Hours	3	11,735	27.3**
	Residual	83	430	
II (Females)	Subjects	11	0.000	0
	Days	1	0.000	0
	Hours	3	13,415	27.4**
	Residual	80	490	

**F 1% = 2.7

† Number modification effect only.

Data from "Endogenous Eosinopenia in Institutionalized Patients with Mental Deficiency" by Halberg, F., Treloar, A. E., Engel, R. and Gully, R. J., A.M.A. Arch. of Neurol. & Psych., in press.

nificant, even with a residue of pooled interactions (only one of which is reduced to zero).

In view of the complicating factors referred to above it is not surprising to encounter reference to "the great variation in circulating eosinophil counts, even in normal conditions, which makes it impossible to establish a base-line" for the study of the physiopathology of these cells.[53] It is indeed impossible to establish a base-line, at least a straight base-line, for eosinophil counts in normal conditions, simply because there is none in normal conditions. There is, however, a regular physiological 24-hour rhythm in number of circulating eosinophils in populations of intact mature mice, dogs, and man, of both sexes, and of different strains, or races, respectively. Both the alternation of rest and activity, and the alternation of relatively high and low eosinophil levels during 24-hour periods, appear to be features of the physiology of certain mammals. The application of the measurement of endogenous variations in the eosinophil level is suggested later in some detail (page 28).[54–56] One should bear in mind, however, that scrupulous care must be taken to maintain the constancy of conditions of observations if reliable results are to be expected from the study of eosinophil levels.[57] Moreover, there are marked species differences in the timing of the 24-hour eosinophil rhythm and perhaps in its mechanism. Data on this periodicity will therefore be examined for each species separately. But it will be necessary first to consider the problem of exogenous eosinopenia.

Certain Aspects of Exogenous Eosinopenia

The intact mammalian organism has been reported to exhibit eosinopenia under a variety of experimental circumstances and after the administration of diverse substances. In surveying the extensive literature on the subject, however, one must keep in mind that, within the physiological range of stimulation and under routine circumstances of observations, the effect of exogenous factors will be influenced by the phase of the 24-hour rhythm. The degree of eosinopenia induced by a potent eosinopenic substance like epinephrine in man varies considerably as a function of the phase of the rhythm during which the observation is made. The change noted four hours following the handling of mice—to cite another example of dependence of response upon phase of rhythm—is a decrease if observations are made during the descending phase of the rhythm, but an increase if they are made during the ascending phase. Obviously any procedure or drug given during the *descending* phase of the 24-hour rhythm will be found to be eosinopenic, unless it has a marked eosinophilic effect. By contrast, a quantitative assay of eosinopenic activity can be based on tests made on intact mice during the *ascending* phase of the eosinophil rhythm. From such tests it is readily apparent that cortisone has a marked eosinopenic effect in doses of several micrograms (figure 1).

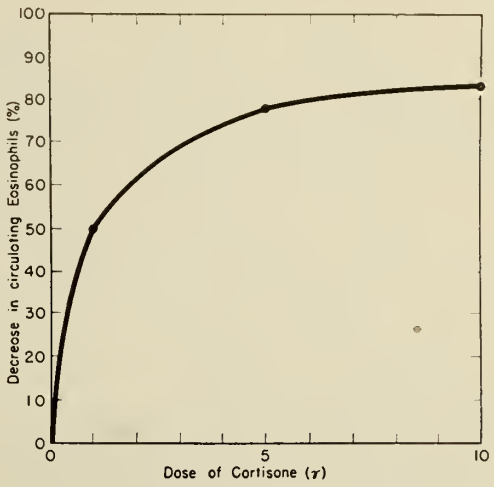

Fig. 1. Dose-response relationship for cortisone-induced eosinopenia (tests) on intact, male one month old CBC mice, made during the ascending phase of the 24-hour eosinophil rhythm.

The per cent change in number of eosinophils of intact male mice over a four-hour period is the index employed in tests for eosinopenic activity. The mice are injected with the material to be tested at the beginning of the ascending phase (at 02:00 under routine circumstances) and counts are obtained for groups of ten mice at four hours post injectionem. Handling for injection does not prevent the rise in number of eosinophils from 02:00 to 06:00. Injection of 0.2 cc. of saline, subcutaneously, may prevent the rise, but does not induce an average fall in number of cosinophils greater than 50 per cent. Cortisone in 5 gamma doses induces a fall greater than 50 per cent in all of the strains of mice examined at the University of Minnesota. The sensitivity of the eosinopenic response in different stocks of mice varies. It was found to be at the 1 gamma dose level for a stock of CBC mice (figure 1), yet it is at or around the 5 gamma dose level for most of the other stocks examined.

Moreover, a response can be defined for adrenalectomized and for hypophysectomized mice which appears to be specific for 11-oxycompounds within the steroid series examined.[58] It is apparent from figure 2 that the steroids which bring about maximal eosinopenia (a 90 per cent decrease in number of circulating eosinophils) at 10 and at 24 hours after the s.c. implantation of 2.8 mg. of material have the following characteristics: (a) they contain 21 carbon atoms in the molecule; (b) they have a side chain of a primary hydroxyl group vicinal to a carbonyl oxygen group (primary alpha ketol grouping); (c) they are unsaturated at C_4; (d) they are either five or four oxygen compounds; (e) they all have oxygen at C_3; (f) they all have oxygen at C_{11}.

The following suggestions are made on the basis of the observations summarized above (figure 2). Maximal eosinopenic activity depends upon the position rather than upon the total number of oxygens in the molecule. All the steroids found to bring about maximal eosinopenia are 11-oxycompounds (marked by a heavy arrow in figure 2). None of the 11-desoxycompounds induces maximal eosinopenia. The alcoholic as well as the ketonic oxygen at C_{11} in the corticoid molecule is compati-

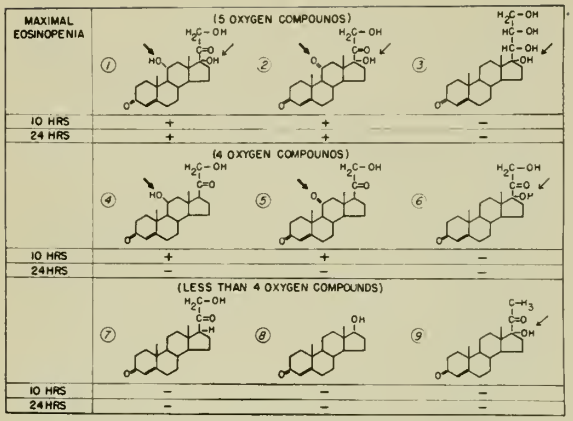

Fig. 2. Some correlations between chemical structure and maximal eosinopenia in adrenalectomized and hypophysectomized mice. 1: △4–pregnene–11(β):17(α):21–triol–3:20–dione (Kendall's Compound F). 2: △4–pregnene–17(α):21–diol–3:11:20–trione (Kendall's Compound E). 3: Homo (ω)–4–pregnene–17(α):20:21:22–tetrol–3–one. 4: △4–pregnene–11(β):21–diol–3:20–dione (Kendall's Compound B). 5: △4–pregnene–21–ol–3:11:20–trione (Kendall's Compound A). 6: △4–pregnene–17(α):21–diol–3:20–dione (Reichstein's Substance S). 7: △4–pregnene–21–ol–3:20–dione (11-desoxycorticosterone). 8: △4–androsten–17(α)–ol–3–one (testosterone). 9: △4–pregnene–17(α)–ol–3:20–dione (17-hydroxyprogesterone).

ble with maximal eosinopenic activity. The relationship between chemical structure and maximal eosinopenic activity is similar to the generally accepted relationship between chemical structure and glycogenic activity in adrenalectomized mice, for the steroid series. The essential requisite for both these effects is the oxygen substitution of the corticoid molecule at C_{11}. Both these effects are enhanced by oxygen substitution at C_{17}, in the presence of oxygen at C_{11}. In the presence of oxygen at C_{11}, oxygen at C_{17} (marked by a light arrow in figure 2), appears to be essential for the prolongation of maximal eosinopenic activity to the 24-hour time point. In the absence of oxygen at C_{11}, the presence of oxygen at C_{17} does not render a steroid maximally eosinopenic.

The above discussion indicates that conditions can be standardized in which the eosinopenic effect is a characteristic solely of the 11-oxycorticoids, *within the steroid series*. The marked eosinopenic effect of epinephrine in adrenalectomized animals points, however, to other direct eosinopenic mechanisms. The inference is made that an autonomic nervous mechanism and an endocrine mechanism, the former illustrated by epinephrine effects and the latter by the effects of 11-oxycorticoids, are both instrumental in the induction of eosinopenia in mammals. Until proof is offered to the contrary it is assumed that within the physiological range of stimulation short-term variations in number of eosinophils are brought about by the nervous mechanism (acting via epinephrine) whereas the 24-hour eosinophil rhythm initiated, perhaps, by epinephrine, is maintained by 11-oxycorticoids.

Endogenous Eosinopenia in Mice

A marked difference between the early night low and the morning high in number of circulating eosinophils from the tail blood of mature male mice has been reported.[59,60*] The difference between the values obtained at the two periods of the day is significant below the one per cent level for all the stocks investigated by the Minnesota group under standardized circumstances.[60] The recurrence of physiological eosinopenia at 24-hour intervals of time is a characteristic of female mice as well as of males.[64] It is noted that these data designate a group phenomenon. The animals were kept in two comparable yet independent groups. A possible effect of the handling of the mice was eliminated by taking only one sample from any given animal.

In other studies blood was sampled twice from each animal in a group for the determination of the number of circulating blood eosinophils. For one sub-group, however, the first count was obtained at night and the second in the morning, whereas the reverse schedule of sampling was carried out for the other sub-group. The differences between the morning high and the night low in number of eosinophils were significant below the one per cent level for both sub-groups.

It appears fair to conclude that the observed eosinopenia is endogenous in its mechanisms and is neither a result of, nor abolished by, the handling associated with sampling blood from mice, although its phase may be modified by experimental procedures.

The necessity for rigid control of the circumstances of observation if reproduceable results are to be obtained in the study of eosinophil levels is best emphasized by the influence of light upon the 24-hour rhythm in number of eosinophils. The original observations on this periodicity in the mouse were made in a room illuminated by artificial light from 06:00 to 18:00. When mice are kept in a room illuminated at night, but dark during the day, the temporal placement of the recurrent eosinopenia within the 24-hour period is shifted approximately 12 hours, within nine days.[65] Making food available for 12-hour periods either during light or during darkness does not prevent this reversal of eosinophil rhythm by a change in illumination. The reversal is not accomplished after three days of reversed light exposure; it is slight at four and five days, and is apparently complete in nine days. The fact that reversal of lighting reverses the eosinophil rhythm regardless of availability of food, and even though the 24-hour variations in the amount of noise in the building which housed the mouse room were not controlled indicates that light plays a more critical role than does either (a) the availability of food or (b) sound in the timing of the eosinophil rhythm in mice.

In mice on dietary calorie restriction kept under routine circumstances of illumination (light from 06:00 to 18:00 and dark from 18:00 to 06:00, regu-

*The occurrence of this phenomenon in mice has been confirmed by Spiers[61] and by Meyer.[62] It has also been ascertained for the rat by Higgins.[63]

lated by automatic switch) the timing of the eosinophil rhythm can be reversed by a change in feeding time. The reversal of timing of endogenous eosinopenia in calorie restricted mice by a change in feeding time appears to occur, however, more slowly than the reversal by changes in lighting.

The delay noted in the reversal of the eosinophil rhythm following the inversion of (a) lighting or (b) feeding could be due to the existence of a complex conditioned reflex mechanism controlling the *timing* of eosinophil rhythm, in which light, and under certain circumstances availability of food, are potent, but perhaps not sole stimuli.

Mice kept in continuous light for nine days cease to reveal statistically significant endogenous eosinopenia. Moreover, this inhibiting effect of light upon the 24-hour eosinophil rhythm is attained without apparent relation to the availability of food. Mice kept in constant light but allowed food only at night, fail to exhibit significant differences in mean number of eosinophils at certain definite periods of the day. It is thus apparent that light, which affects the timing of the eosinophil rhythm so profoundly, has also an inhibitory effect on the rhythm itself.

By contrast, mice kept in constant darkness for periods of time up to thirteen days show a marked eosinophil rhythm which is comparable in timing to that of mice under conditions of 12-hour darkness alternating with 12-hour light. This persistence of the eosinophil rhythm in the absence of light suggests that light is not required for its maintenance and for its persistence. It is conceivable, though not proved, that the mechanism which maintains the 24-hour eosinophil rhythm depends on darkness. Mice kept in continuous darkness for nine days after a previous exposure to continuous light for the same period of time fail to redevelop an eosinophil rhythm. By contrast, mice returned to an alternating light-dark schedule for nine days, after a previous exposure to continuous light for an equal period of time regain the eosinophil rhythm. Although the important question of a mechanism remains unanswered by these studies, the data nevertheless seem to indicate that light is needed in mice to establish rhythmicity, but darkness is needed for its maintenance and persistence.

Attention should be directed to the marked similarities in the effects of light on the eosinophil rhythm and on the rhythm in bodily activities in mice:

1. Reversal of lighting reverses the timing of the activity rhythm[15] as well as that of the eosinophil rhythm.

2. This reversal by lighting requires several days for both rhythms.[65,15,66]

3. Light has an inhibitory effect on the activity rhythm[15,66] corresponding to its effect on the eosinophil rhythm.

4. Rhythmic activity continues in mice kept in constant darkness.[15] So does the 24-hour eosinophil rhythm.

5. Since the mouse is a nocturnal animal its peak in bodily activities occurs at night.[15,66,67] Physiological eosinopenia occurs also at night—in mice which have not been exposed to extraordinary stimulation.

The question may therefore be raised whether normal activity is capable of exciting the same structures and physiological mechanisms as are activated by extraordinary exogenous stimuli. If normal activity could be shown to have this function, it would provide the necessary control for the investigation of the effect of extraordinary exogenous stimuli.

It is noted that a difference, perhaps resulting from a mechanism similar to that inducing eosinopenia, has been reported for the lipid content of the adrenal cortex in white mice killed at two different times of the day.[67] In mice killed at 09:00 the zona fasciculata was filled in toto with lipid. In mice killed at midnight the lipid did not extend beyond the outer third of the fasciculata. It appears to be of further interest that 24-hour periodicity in the glycogen content of the liver has been observed in mice,[68-73] and in other mammals,[74-84] including man.[85] On the average, glycogen levels decrease during the ascending phase of the eosinophil rhythm. It is conceivable that corticoids, which induce a decrease in number of eosinophils, may control glycogen deposition in the liver under routine circumstances and ad libitum feeding. Nevertheless, it must be remembered that the parallelisms between a possible rhythmic activity of the adrenal cortex on one hand and (a) the glycogen rhythm, (b) the eosinophil rhythm and (c) the rhythm in bodily activities on the other hand do not necessarily imply causal connections.

Unfortunately, the classical endocrinological approach to the problem of the eventual role of adrenal cortical function as a mechanism of 24-hour periodicity in mice yields occasionally inconsistent results. Removal of the gland is not always associated with a complete loss of periodicity in number of eosinophils. The inhibition of the eosinophil rhythm after adrenalectomy may be incomplete perhaps as a result of additional (heterotopic) adrenal cortical tissue not removed at operation. Moreover, it is evident that the absence of rhythm in number of eosinophils does not necessarily imply the absence of non-rhythmic variations. Variations brought about by extra-adrenal factors occur at random in mice and in man. The effect of extraadrenal factors can be minimized, however, by the standardization of the circumstances of observation. Correspondingly, the effect of heterotopic adrenal tissue can be minimized by employing a large sample size and by taking into account survival rates after the operation. When the above precautions are taken, the suppression of the eosinophil rhythm by adrenalectomy can be demonstrated for mice as well as for man (see below).

Certain Methodological Implications Resulting from the Recognition of the 24-Hour Eosinophil Rhythm in Mice

1. Recognition of the 24-hour eosinophil rhythm in the mouse permits the determination of eosinophil levels that are characteristic for certain stocks of mature inbred mice of both sexes, provided that care is exercised to maintain constancy of conditions of observation.[57] The differences between groups of C_{57} Black and A mice, to cite an example, are very considerable ($P < .001$).

2. The detection of a marked eosinopenia of the third week of pregnancy and of the period immediately following delivery (48 hours postpartum) is mentioned as another observation which stands out clearly as a consequence of an experimental design taking into account 24-hour periodicity.[59] Disregard of 24-hour periodicity would have obscured the phenomenon under investigation. The evening level of non-pregnant C_3H females is on the average equal to the morning level of animals of this stock pregnant two weeks or more.

3. A higher relative specific activity of phospholipid phosphorus and of pentosenucleic acid phosphorus from liver microsomes was noted in materials obtained during a period associated with a low eosinophil level than in materials obtained at the time of a high eosinophil level.[86] Determination of the eosinophil rhythm in studies on intracellular metabolism for the determination of certain phases of metabolism within the 24-hour period may likewise prove of use in other studies. It is noted that 24-hour periodicity in tissue desoxypentosenucleic acid has been mentioned recently by Kelly et al.[87]

Endogenous Eosinopenia in Dogs

Despite the large variations in eosinophil count among individual mongrel dogs there is a marked decrease in eosinophil levels during the morning hours. This change is statistically reliable ($P < .01$). Endogenous morning eosinopenia appears to be a characteristic of groups of mature dogs of both sexes.[88]

Endogenous Eosinopenia in Man

Definite changes throughout the 24-hour period in the number of circulating eosinophils in man have been described repeatedly.[89–93] Their significance, however, has been obscured among other factors by the very considerable variability of eosinophil counts, in the absence of standardization (see page 24). By contrast, standardization of circumstances of study, especially of bodily activities, shows the occurrence of an endogenous eosinopenia of humans which is comparable in extent and in regularity to that seen in mice. On the average, the night levels in number of eosinophils in man are considerably higher than the day levels.[89–92,55] The transition from the night "high" to the morning "low," the endogenous morning eosinopenia, is the most characteristic phase of the 24-hour eosinophil rhythm in man.

Endogenous eosinopenia in man, as well as in dogs and in mice, appears to be related to initiation of daily activities. The decrease in number of eosinophils from 06:30 to 09:30 of the same morning was noted in populations habitually arising around 07:30. In subjects whose daily activities have been initiated for years at 06:00, endogenous eosinopenia occurs approximately 90 minutes earlier than in subjects who get up around 07:30. The hypothesis that endogenous eosinopenia actually occurs earlier in subjects who get up earlier is in keeping with the statistical findings: (a) the lack of significance for the change in mean relative eosinophil level from 08:00 to 09:30 in subjects who get up at 06:00, and (b) the absence of change in mean relative eosinophil level from 05:00 to 06:30 in subjects who get up at 07:30. An inference that decrease in number of circulating eosinophils is related to initiation of daily activities seems appropriate. It is corroborated as a more general relationship between two variables exhibiting 24-hour periodicity by the species differences in the timing of endogenous eosinopenia between man and dogs on one hand and mice on the other. Man and dogs, more active during the day than at night, show eosinopenia in the morning. Conversely, mice, active mainly during the night, show eosinopenia in the evening and early night.

As for the mouse, the question may again be raised for man, whether daily activities constitute a physiological stimulus capable of exciting the same structures and mechanisms as are activated by extraordinary exogenous stimulation. In man, as in the mouse, endogenous eosinopenia shows synchronization with changes in variables, some of which are currently accepted as indices of adrenal cortical function. An increase after awakening in the urinary excretion of 17-ketosteroids and in that of neutral reducing lipids, as well as a decrease in number of circulating blood lymphocytes, has been reported.[94–97] An increase during the morning hours in the urinary excretion of corticoids (determined after hydrolysis with glucuronidase) and in the number of circulating blood neutrophils has been noted by the University of Minnesota group. Although this writer failed to ascertain a correlation between the morning changes in 17-ketosteroid excretion and in number of eosinophils, *for the same individual,* as *group phenomena,* these two periodicities show an inverse trend (figure 3).

In summary, then, a number of physiological changes in circulating blood characterize awakening in man. Some of the variables in which these changes occur (i.e., numbers of eosinophils and lymphocytes) are known to be controlled, in part, by certain adrenal cortical hormones. Moreover, there is a marked increase during the morning hours, in the urinary excretion of certain steroidal substances related to these hormones. It appeared therefore worthwhile to test the hypothesis that the 24-hour rhythm in number of eosinophils and possibly some of the associated 24-hour periodicities in man are controlled by periodic changes in the rate of

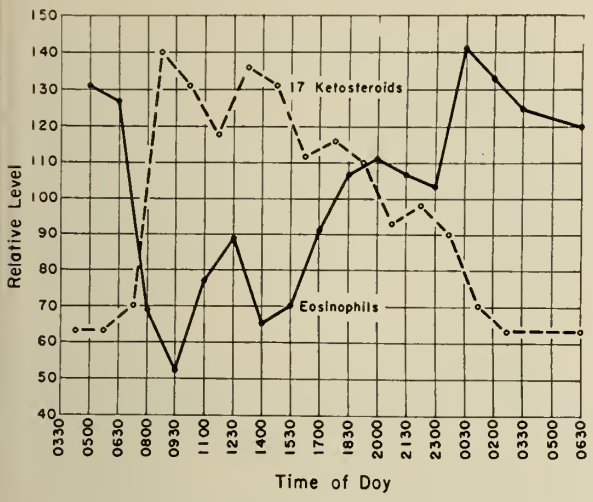

Fig. 3. Twenty-four-hour rhythm in the circulating eosinophils, and variations in the excretion of 17-ketosteroids. The relative eosinophil curve was computed from the data obtained by the author on 17 medically normal males. The relative 17-ketosteroid curve was computed from the data of Mickelsen, O., E. v. O. Miller and Ancel Keys on four medically normal males, one of them studied over two 24-hour periods (prepared for publication by Mickelsen, O., E. V. O. Miller and Ancel Keys from the Laboratory of Physical Hygiene, University of Minnesota Medical School). See also: Miller, E. v. O., Mickelsen, O. and Keys, A., Fed. Proc. 6:279, 1947.

secretion of adrenal cortical hormones. The classical concepts of endocrinology require, in the first place, evidence that a phenomenon assumed to be correlated with the activity of a ductless gland should be absent when this gland has been removed. This criterion is met by the demonstration that patients with (a) surgical bilateral adrenalectomy, (b) Addison's disease, and (c) panhypopituitarism do not exhibit a 24-hour rhythm in number of circulating eosinophils, under circumstances which are comparable to those under which such a rhythm has been

Fig. 4. Variations during the 24-hour period in mean relative eosinophil levels in man (Group 2: — — — — — — unlimited activity; Group 1: – – – – – – limited activity; Group 3: ——— limited activity—adrenal insufficiency).

demonstrated in mature subjects with a functioning adrenal gland[53,98] (figure 4). The second criterion for the demonstration of endocrine mechanisms in biological phenomena consists of the ability to induce changes attributable to the activity of a ductless gland by the administration of certain of its products after removal of the gland. It is recalled that cortisone in doses of 5γ/25 gm. mouse reverses the ascending phase of the eosinophil rhythm. Moreover, maximal eosinopenia can be obtained in adrenalectomized mice subsequent to the administration of 11-oxycorticoids. The specificity of this effect appears to be established within the corticoid series by the failure of certain other steroidal substances to induce this phenomenon. Although a variety of other non-steroid materials equally failed to induce the phenomenon (eosinopenia) under controlled circumstances, it must be remembered, nevertheless, that the non-steroid epinephrine does so. A morning increase in the level of circulating epinephrine in man which has been reported[99] is therefore of interest. It is conceivable, although not proved, that the morning changes in the physiological variables discussed are initiated by and constantly modified by the autonomic nervous system (via epinephrine) in the shocks and alarms of daily experience. The conception suggested here resembles Cannon's principle of homeostasis[100] with the important difference that the base-line about which variations are held to occur is not the straight line (and its range of "common variation") which has been postulated since Claude Bernard developed the concept of the constancy of our internal environment. The "base-line" is rather the *curve* of a 24-hour cycle, an essential part of bodily function and thus of physiology. It will be realized that the recognition of this 24-hour cycle calls for a new methodological approach to the investigation of "stress" phenomena. These can be adequately quantified and controlled only when data are interpreted as variations from a 24-hour curve rather than from an assumed horizontal line.

From a theoretical point of view, despite modulation by autonomic nervous effects, a 24-hour adrenal cortical cycle deserves serious consideration as the mechanism possibly underlying our adaptation *to* our daily activities, and perhaps our preparation *for* them. Just as the sexual cycle describes endogenously regulated changes preparatory to copulation and subsequent fertilization, the 24-hour cycle may describe the process of preparation for each activity in the life of animals and man, necessary for day to day survival. The many similarities between the eosinophil and the activity rhythm in mice and in man are in keeping with this hypothesis, suggested by the data on the adrenalectomized man. Just as the preparation of smears from the fluid content of the vagina enables the observer to follow the cyclic and other changes of the vaginal and cervical epithelium, the determination of endogenous changes in number of circulating blood eosinophils has proved a simple and dependable method for the evaluation

of a 24-hour adrenal cortical cycle in mice[54] and in man[55,56] The 24-hour cycle resembles the sex cycle in being controlled by steroidal hormones. It differs, however, in its persistence under circumstances known to suppress the sex cycle (i. e., of 50 per cent reduction in dietary carbohydrate and fat).[54] It might be concluded that the 24-hour adrenal cycle is the biologically more essential mechanism.

IV. Comment

Certain aspects of 24-hour periodicities in adrenal activity, in mitotic activity and in the occurrence of epileptic seizures bear a striking relationship to the phases of bodily activity and inactivity. The temporal placement of the eosinophil rhythm and of the mitotic rhythm within the 24-hour period could conceivably be controlled by physiological shifts in pituitary function from the production of STH (growth hormone, influencing mitoses, perhaps) to that of ACTH (adrenocorticotropic hormone, controlling the changes in rate of secretion of certain corticoids). Under this assumption, STH and ACTH would play a role within a 24-hour cycle comparable to that of FSH and LH within the sex cycle. But whether governed by ACTH and STH or by other controlling mechanisms, disturbances in this physiological sequence should be studied as deviations from a physiological cycle rather than as deviation from an imaginary "base-line." For the "awakening type" of epileptic a thorough understanding of 24-hour periodicity might prove to be of considerable significance for our understanding of the etiology of this disease. Results of an exploration of the complex factors influencing the periodic changes in mitotic rate may prove valuable for cancer research. This discussion as a whole, however, is guided only by the desire to present certain prominent illustrative examples of work in various fields which have the common characteristic of suggesting the importance of further research into the mechanisms of 24-hour periodicity. Complete understanding must await the results of further work.

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The writer is indebted to Dr. Maurice B. Visscher, head, Department of Physiology, University of Minnesota, for advice as well as for the privilege of straying far beyond the confines of an original problem and thus for an opportunity to explore the eminently physiological problem of the mechanism of 24-hour periodicity in mammals. Paul C. Royce, M.B., helped in assembling and in discussing some of the material presented in this paper. The unceasing interest during several years as well as the invaluable help of a respected friend, Professor Henry Nash Smith of the Department of English, University of Minnesota, is deeply appreciated.

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Lancet Editorial

The Future and the Criminal

An article in this issue of The Journal-Lancet by Dr. Keith Simpson draws attention in a most interesting fashion to certain medical aspects of crime. It is axiomatic that one cannot consider crime without considering the criminal who performs it. The past fifty years have seen numerous advances in penology, and at the bottom of this progress is the corner stone of a shifting attitude which looks not alone to the punishment of the criminal but also toward the ideal of his rehabilitation so that he may again take his place among his fellow men as a useful citizen. For from one point of view the violation of the laws of society may be looked upon as social sickness. If this be a correct concept, the physician should have some contribution to make in the field of illness. The sparse amount of valid research on criminal behavior indicates that some, at least, of the persons who commit anti-social acts suffer from illnesses which are clearly medical, usually psychiatric in nature. Thus, a man with paranoid psychosis shoots a University student in a drug store, feeling that his life is in danger. Or a similarly ill man kills a secretary because the learned society for which she works would not accept his bizarre paper on the prolongation of life. A depressed mother kills her two children because she feels, in her delusional state, that it is kindness not to let them suffer as she is sure they must.

While most crimes are not committed by ill people whose diseases are so readily recognizable, there is a growing feeling that the humane management of the criminal and the better protection of society requires further revision in our planning and in our laws. In our present state of knowledge we perhaps cannot undertake to treat successfully a large percentage of persons convicted of major crimes, but to make a beginning with the knowledge and skills we do have is not only possible but practicable. Planning for the future will involve the principle of creating within our penal institutions well staffed clinical facilities which can adequately study and diagnose the criminal, and make recommendations for therapy for those who are treatable by known methods. Sentences for major crimes might be indeterminate, discharge depending upon treatability rather than upon some fixed sentence which often finds the prisoner on discharge just as liable to repeat his crime as when he was arrested. Such clinical facilities within our penal institutions should also serve the all important purpose of research and should aid materially in pushing forward the frontiers of knowledge in areas that are mapped only vaguely at the present time.

Successful progress in these directions will require the planning and the skills of legislators, judges, lawyers, penologists, sociologists, and the medical profession with its associates such as social work and psychology. It seems inevitable that such progress must come, not only for reasons that are humane and kindly but also because of down-to-earth considerations on the part of the community as it seeks to prevent criminal behavior with its saddening wastage of constructive human accomplishment and effectiveness and as it attempts to return as many people as possible to useful life from our prisons.

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Bone Tumors, by Louis Lichtenstein, M.D., senior pathologist, General Medical and Surgical Hospital, Veterans Administration Center, Los Angeles, 1952. St. Louis: C. V. Mosby Co. 315 pages. $10.50.

This book, written by an outstanding authority on bone pathology, is a summation of the author's long study of primary bone tumors carried out at the Hospital for Joint Diseases in New York. Following a presentation of his classification of tumors of bone, Dr. Lichtenstein discusses each type in regard to clinical, roentgenologic, pathologic and treatment aspects. A helpful feature is a concise summary of each entity following the detailed discussion. An appendix on non-neoplastic lesions which simulate bone tumors is an added feature.

The book is well illustrated with excellent photomicrographs and roentgen film reproductions. It will be of particular value to those interested in bone disease and to the student who wishes a concise reference for study or review.

G.M.H.

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A Textbook of Orthopedics, with a Section on Neurology in Orthopedics, by M. Beckett Howorth, M.D. Philadelphia: W. B. Saunders Co. 1,110 pages. $16.00.

This attractive book of 1,110 pages evidently represents a lifetime of work. As the author says, it is based on twenty years of experience. Every type of orthopedic problem is well discussed. In addition, there is a fine section on neurology in relation to orthopedic practice, written by Fritz Cramer. This addition is doubtless a good one because neurologic injuries commonly result in orthopedic problems, and often a neurologist and an orthopedist must work together.

All medical readers, and certainly all orthopedists will be grateful to Dr. Howorth for the remarkable first chapter on the history of orthopedics. There one finds pictures of the men who in the past contributed so much to the knowledge of this subject. There is also a very fine bibliography on the history of orthopedics. W.C.A.

Progress in Neurology and Psychiatry, E. A. Spiegel, editor, volume VII, 1952. New York: Grune and Stratton. 604 pages. $10.00.

This book contains a concise review of the current literature in the field of neurology and psychiatry. The material is well organized and simply presented. In this volume new sections have been added on pediatrics neurology, genetics and criminal psychiatry.

The first five chapters, covering the field of basic neurology and including such subjects as the anatomy, pathology, physiology and pharmacology of the nervous system, should prove most useful to the student and specialist. The remainder of the book is clinically oriented and contains excellent reviews with special emphasis on diagnosis and treatment. This latter material should be most useful to the practicing physician who is constantly confronted with illnesses implicating the nervous system and who would like to have access to the most current views regarding diagnosis and treatment. The reviews are for the most part presented in an unbiased manner, the only exception being the section on neurosyphilis, in which the authors are so fixed on their own convictions that they find it impossible to be objective about results of others which might be contrary to their own ideas.

This book certainly can be highly recommended to the profession as an excellent addition to the reference library. A.B.B.

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Advances in Medicine and Surgery, from the Graduate School of Medicine of the University of Pennsylvania. Philadelphia and London: W. B. Saunders Company. 441 pages.

The volume *Advances in Medicine and Surgery* is a collection of papers presented in a series of symposia by the Graduate School of Medicine of the University of Pennsylvania. The symposia include the following subjects: Present Status of Adrenal Cortical Hormones, Role of Potassium in Health and Disease, Hypertension: Newer Aspects of Medical and Surgical Treatment, Newer Concepts in Preoperative Evaluation and Preparation of Patients, Thromboembolism, Pulmonary Infections, Relief of Pain, Current Status of the Cancer Problem, Recent Developments in Viral Diseases and Functional Disorders. Altogether there are 53 papers by 55 contributors.

The material in these symposia is well organized and the current advances in our medical knowledge are presented. Subjects are documented from the fundamental and clinical approach. A bibliography is included with each paper.

This book presents a good basic education in the subjects of the ten symposia selected by the Faculty of the Graduate School of Medicine.

E.R.A.

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Inhalation Anesthesia, a Fundamental Guide, by Arthur E. Guedel, 1951. Second edition. New York: Macmillan Company. 143 pages. $3.75.

This is a brief, well written book on the essentials of anesthesia. The writer describes some peculiar cases of sudden death in two of which the cause appeared to be fear.

W.C.A.

•

Heart Disease, Its Diagnosis and Treatment, by Emanuel Goldberger, M.D., 1951. Philadelphia: Lea & Febiger. 651 pages, 229 illustrations. $10.00.

The author of this volume is well known to everyone interested in heart disease for his outstanding work in the development of unipolar electrocardiography, and his book on the subject.

In the present volume, however, the bedside diagnosis and treatment of heart disease are stressed. Full coverage is given also to the latest advances in the use of technical methods, such as electrokymography, ballistocardiography, angiocardiography and catheterization of the heart. Latest advances in treatment are also fully covered.

The book is written in a clear and interesting style and should be a welcome addition to the library of both the general practitioner and specialist, as a ready reference on the subject of heart disease.

T.Z.

American College Health Association News . . .

Requests for the thirtieth annual Proceedings have been received from individuals and groups other than our membership. We are sorry that requests could not be filled because for the first time the supply of the report is exhausted. This fact is proof that the Boston meeting was an unusual and outstanding one and that the Association and its annual publication are known.

* * *

The secretary has received copies of blue prints of the health service plans from several member institutions. We take this opportunity to express our appreciation to these directors for providing the copies. The two file copies which were collected several years ago are in constant use. We hope that additional building plans will be forwarded to us by many other institutions, both large and small.

* * *

The Illinois Section has conducted an active membership campaign. As a result, three Illinois institutions have been approved for membership by the executive committee.

Bradley University, Peoria, is a privately endowed institution accredited by the North Central Association of Colleges and Secondary Schools. The University has an enrollment of 1,993 men and 654 women. Harold A. Vonachen, M.D., the director of the student health service, serves part time. He is assisted by a full time nurse, a health educator, and a sanitarian. A. G. Haussler, the vice-president and health educator, is authorized to represent the institution in this Association.

The *Illinois Institute of Technology*, Chicago, a former member, is a private institution accredited by the North Central Association of Colleges and Secondary Schools. James P. Fairbairn, M.D., is the part time medical director and Elizabeth Blaeser, R.N., the full time nurse. The total enrollment is almost six thousand students, over half of whom are evening and special students.

Illinois Wesleyan University, Bloomington, a denominational institution with an enrollment of 377 men and 293 women, is accredited by the North Central Association. Velma J. Arnold, R.N., is the director of the Health Service, and she and Marian Niehaus, the health educator, are authorized to represent the department.

* * *

Report of staff changes—

Wilder P. Ellis, M.D., is the director of the health service at the College of Wooster, Wooster, Ohio.

Roxie A. Weber, M.D., is director at the Oklahoma Agricultural and Mechanical College at Stillwater, Oklahoma. The other members of staff are Dr. J. O. Burner and Dr. R. R. Riggs.

Kollbjorn Jenssen, M.D., Oslo, and Oystein Vinje, M.D., Kristiansand, Norway, have joined the staff of the University of Kansas Health Service for one year on a fellowship basis. These physicians are graduates of the Medical School, Oslo, Norway.

R. William Cheney replaces Erastus W. Pennock as director of Student Health Service, Springfield College, Massachusetts.

Llewellyn Sale, Jr., M.D., is the new director of the Health Service at Washington University, St. Louis, Missouri. This institution, with an enrollment of 11,000 students, has a staff of five part time internists, a part time surgeon, a part time orthopedist, a half time psychiatrist, two part time and two full time graduate nurses, and a secretary.

Amelia Natale, M.D., who graduated from Hahnemann Medical College in Philadelphia, is a new staff member at the Pennsylvania State College, State College, Pennsylvania. She works with Anna O. Stephens, M.D., chiefly with female students on the campus.

* * *

Mildred L. Crane, R.N., at Atterbein College, Westerville, Ohio, is assisted by three nurses who are completing their academic training for a B.S. degree. This college of approximately seven hundred students has a ten bed infirmary in addition to an outpatient clinic.

* * *

The Pacific Coast Section held its 16th annual meeting at Stanford University on November 28 and 29. Approximately 69 persons were registered. The following officers were elected: President—Dr. Gilbert S. Coltrin, the Associated Colleges of Claremont; president-elect—Dr. Paul O. Greeley, University of Southern California; secretary-treasurer—Mrs. Ruby Burgar, Occidental College; members at large—Miss Margaret Twombly, San Jose State College, for a two year term, and Dr. Edith M. Lindsay, University of California, Berkeley, to complete the one year term left vacant by Dr. Greeley.

The highlights of the program were:

"Diphtheria and Diphtheria Immunization in an Adult Population," Henry D. Brainerd, M.D., associate professor of clinical medicine, University of California Medical School at San Francisco.

"Effects of ACTH in Severe Infectious Mononucleosis," Charles E. Bender, M.D., physician, student health service and clinical instructor in medicine, University of Washington.

"Who Should Treat Acne Vulgaris," Frances M. Keddie, M.D., assistant clinical professor of dermatology, University of California Medical School at San Francisco.

"A Philosophy for Student Health Services," Oliver E. Byrd, Ed.D., M.D., professor education and director of the department of Hygiene, Stanford University.

"Changing Objectives in Student Health Work," Charles E. Shepard, M.D., professor of hygiene and consultant to the health service, Stanford University.

"Role of Physical Medicine in Student Health Service," William Northway, M.D., professor medicine, School of Medicine, Stanford University .

"Industrial Hazards in the Laboratory," James L. Born, M.D., Donner Laboratory, University of California.

"Radiation Hazards," Nelson B. Garden, E.E., supervisor of radiation safety, University of California.

"Some Remarks on Leonardo da Vinci," Charles D. O'Malley, Ph.D., Department of History, Stanford University (guest speaker).

Medical Records of Student Health Services: "Out Patient Records," Hanna Kraus, R.R.L., Medical Records, Student Health Service, University of California at Los Angeles; "In Patient Records," Glen Gibson, R.R.L., Medical Records, Student Health Service, University of California.

"The Nurse's Role in a Student Health Service," Ardath Thompson, R.N., Student Health Service, University of California.

"Medical Social Service in a Student Health Program," Mrs. Marian W. Moore, Medical Social Service, Student Health Service, University of California.

News Briefs . . .

North Dakota

WRITTEN EXAMINATIONS for North Dakota state medical licenses are scheduled for January 7, 8 and 9 in Grand Forks, North Dakota. Dr. C. J. Glaspel of Grafton, secretary of the North Dakota State Board of Medical Examiners, is in charge of arrangements.

° ° °

DR. R. H. WALDSCHMIDT, Bismarck, has received an appointment to the board of governors of the American College of Surgeons as the representative from North Dakota. Dr. Waldschmidt succeeds Dr. A. C. McCannel of Minot, who served on the board for several years.

° ° °

THE medical staff at Minot's veterans administration hospital has been reduced to two members. Other additions to the medical staff are being sought. Because of the shortage of physicians, the patient load was trimmed to a maximum of 45 last October. The institution is rated as a 162 bed hospital, but was run at half-capacity until the October reduction. Currently, the hospital has an average patient load of about 40 patients.

° ° °

DR. DAVID DICKINSON, head of the respirator center of the National Foundation for Infantile Paralysis at Ann Arbor, spoke on the diagnostic techniques in treatment of respirator cases of poliomyelitis at a dinner meeting on December 16 in Fargo.

° ° °

GUEST SPEAKERS at the Southwestern District Medical Society meeting at Dickinson on December 6 were Dr. A. V. Stoesser, department of pediatrics at the University of Minnesota and Dr. Norman Nelson, department of internal medicine, both of the University of Minnesota. Dr. Stoesser spoke on "Differential Diagnosis and Treatment of Respiratory Diseases in Children" and Dr. Nelson on "Psychosomatic Medicine."

° ° °

DR. EDMUND G. VINJE, Hazen, was named 1953 president of the Sixth District Medical Society at a meeting in Bismarck on December 2. Other officers are Dr. Ernest Salamone, Elgin, vice president, and Dr. C. H. Peters, Bismarck, secretary-treasurer. Dr. Vinje is director of the North Dakota Tuberculosis and Health Association and a counselor of the Mississippi Valley Tuberculosis Association.

° ° °

New locations and appointments . . .

DR. DOUGLAS T. LINDSAY, a graduate of the University of Minnesota, and formerly with the North Dakota Crippled Children's Service, has joined the Fargo Clinic in the department of orthopedic surgery.

DR. RALPH VINJE, a graduate of the Northwestern University Medical school, has opened practice limited to orthopedic surgery and surgery of the hand, in Bismarck, North Dakota.

DR. T. BLACKSTEIN of Winnipeg, a graduate of the University of Manitoba, has joined the staff of the McKenzie County Memorial hospital in Minot.

DR. E. R. WASEMILLER, a member of the staff of the Wahpeton Clinic, has reported for duty as a medical officer in the navy.

DR. DAVID JAEHNING, recently discharged from the Air Force medical service, has assumed practice in Wahpeton, where he will be associated with Dr. E. J. Beithon.

DR. JAMES V. MILES, who has been in the armed forces medical corps at Camp Rucker, Alabama, has returned to Jamestown and resumed his position with the DePuy-Sorkness clinic.

DR. MARTIN H. ZWERLING, a graduate of Long Island college of medicine, has joined the staff of the Quain and Ramstad clinic at Bismarck as an eye, ear, nose and throat specialist.

DR. F. W. FORD, a graduate of Tufts Medical school in 1935, has joined the staff of the Harvey Medical Center as a specialist in surgery.

DR. JAMES F. HARRINGTON, a graduate of the St. Louis School of Medicine, will practice in Mandan as an associate of Dr. Philip L. Blumenthal.

Minnesota

GIFTS totaling approximately $300,000 for research and scholarships at the University of Minnesota have been announced by the board of regents. Dr. John Wild was granted $21,616 to perfect instrumentation for the echograph, the ultrasonic device for detecting cancer by high frequency sound waves. Dr. F. John Lewis was granted $6,370 for additional experimental cardiac surgery.

Also sharing in the $102,000 in cancer grants from the USPHS are Dr. I. M. Kolthoff, professor of analytical chemistry, $30,660; Dr. George Moore, cancer coordinator, $25,000 for teaching and clinical work; Dr. Jerome T. Syverton, head of the department of bacteriology, $15,000 for research on mouse mammary cancer; and Dr. Saul Cohen, associate professor of physiological chemistry, $10,495.

Recipients of other large grants include Dr. Frederic Kottke, head of the department of physical medicine, $18,078; Dr. Maurice Visscher, head of the department of physiology, $15,755; Dr. Victor Lorber, $10,000; Dr. Richard Varco, who collaborated on the refrigerated heart operation, $9,996; Dr. H. C. Lichtenstein, associate professor of bacteriology, $9,532; Dr. W. G. Kubicek, associate professor of physical medicine, $9,093; Dr. J. F. Hartman, associate professor of anatomy, $8,721, and Dr. Yoshio Sako, fellow in surgery, $7,036.

° ° °

THE new Burns Memorial building at Anoka state hospital was recently dedicated to the late Dr. Herbert A. Burns who died July 8, 1949. Dr. Burns, long an advocate of a central treatment center for Minnesota's mentally ill who also have tuberculosis, was former tubereulosis control officer for state institutions and superintendent of the state sanatorium at Ah-gwah-ching.

° ° °

A TV program on Minnesota's tubereulosis problems, held on November 16, featured three Minnesota doctors nationally known in tuberculosis work: J. A. Myers, chairman of the board of editors of THE JOURNAL-LANCET; John Briggs, chief of medicine at Ancker hospital, and Ezra V. Bridge, superintendent of Mineral Springs sanatorium.

° ° °

DR. S. ROBERT MAXEINER, JR., who recently completed his surgical fellowship at the Mayo Clinic, Rochester, on July 1, has entered the marine service and is now with the marines in Korea.

° ° °

THAT a "broken-down, one-story wooden building in a Cuban cornfield" that was one of the great "battlefields"

(Continued on page 38)

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NEWS BRIEFS—(Continued from page 36)

of medical history was dedicated on December 3 as a monument of Dr. Walter Reed is due in part to the efforts of Dr. Philip S. Hench of the Mayo clinic. In 1940 he "rediscovered" the building where a group of volunteers helped Reed prove that yellow fever was transmitted by mosquitoes and since then he has been a leader in the fight to save it.

* * *

GOVERNOR C. ELMER ANDERSON has been invited to nominate a 75 year old Minnesota physician to represent the state at the first western hemisphere conference of the World Medical association which will be held next April at Richmond, Virginia.

* * *

DR. KARL D'A. ANDRESEN has been named new president of the Asbury Hospital medical staff for 1953. Dr. Robert B. Potter is vice president and Dr. Virgil J. P. Lundquist, secretary-treasurer.

* * *

DR. MILDRED SCHAFFHAUSEN, an intern at General hospital, Minneapolis, was recently named "outstanding woman medical student in the nation" by the American Women's Medical Association. She received a rating of 97.5 in national competition.

Deaths . . .

DR. PAUL H. BURTON, 76, Kenmare's first doctor, and for nearly fifty years practicing physician at Fargo, North Dakota, died November 5 in Fargo. After graduation from the University of Minnesota about 1901 he practiced for a time at Hallock and Red Lake Falls, Minnesota. He continued as a private practitioner in Fargo until 1925, when he helped to found the Dakota clinic. DR. GEORGE E. HEINZEROTH, 77, for many years a physician in Turtle Lake, North Dakota, died in Bismarck on November 5.

* * *

DR. FRANCES EATMAN ROSE, an early Fargo physician and surgeon, died recently in Spokane, Washington. After her graduation from the University of Minnesota she began practice in 1895. After her marriage, she moved to Spokane in 1906. She joined the staff of St. Luke's hosptial in Spokane and was a member of various medical and surgical societies.

* * *

DR. GEORGE R. WALDREN, 53, Cavalier, North Dakota, died on November 25. After receiving his medical degree, he practiced with his father, the late H. M. Waldren, before going to Pembina, then later to Cavalier.

* * *

DR. L. J. SEIBEL, 60, Harvey, North Dakota, died suddenly December 6.

* * *

DR. RUTH GERTRUDE NYSTROM, Minneapolis, a former member of the Minneapolis General hospital staff, died December 12, after an illness of about three years. A graduate of the University of Minnesota in 1928, Dr. Nystrom specialized in neuropsychiatry, gynecology and obstetrics.

* * *

DR. WILLMAR C. RUTHERFORD, 66, former St. Paul physician, died December 21 at West Palm Beach, Florida. A graduate of the University of Minnesota and Marquette university, Dr. Rutherford had practiced in St. Paul from 1911 to 1946, when he moved to Nisswa, Minnesota, and opened an office at Brainerd. During World War I Dr. Rutherford helped organize Army Field Hospital 135 of the Minnesota national guard.

(Continued from page 19)

extent. The serum sodium disturbance in cerebrovascular accidents occurs early and not as a remote complication.

Disorientation and stupor occur as specific sequelae of adrenal insufficiency particularly after the administration of parenteral fluids without the administration of adrenal cortical substances. This is particularly true when glucose and distilled water are given.

The possibilities for the causation of adrenal insufficiency are many. Tuberculosis is the most common. Adrenal atrophy is another cause. Various tumors and Hodgkin's disease have caused adrenal insufficiency.

I wouldn't be surprised if he had hepatic cirrhosis as an incidental finding at autopsy.

DR. EBERT: Would you consider miliary tuberculosis?

DR. FLINK: I did, but the fever could occur with adrenal insufficiency alone.

DR. HAMMARSTEN: There are eight students here today and they had six different diagnoses. Three thought the patient had Addison's disease.

DIAGNOSES

Clinical diagnosis: Cirrhosis with bacteremia? Abdominal lymphoma? Cerebral thrombosis, old.

Dr. Flink's diagnosis: Acute adrenal insufficiency due to tuberculosis of the adrenal gland. Possible cirrhosis? Cerebral thrombosis, old.

Anatomical diagnosis: Adrenal insufficiency. Tuberculosis of lungs, adrenal glands, and lymph nodes. Cerebral arteriosclerosis. Cholelithiasis.

PATHOLOGICAL DISCUSSION

DR. GLEASON: There was caseous tuberculosis occupying the upper half of the left lung. The spleen weighed 350 gm. There were calculi in the gallbladder. The left adrenal weighed 50 gm. and the right adrenal 25 gm. They were completely replaced by caseous necrosis. The periaortic lymph nodes were enlarged and had foci of caseous necrosis. The brain had multiple small cystic areas in the region of the basal nuclei. There was cerebral arteriosclerosis but no thrombosis.

Microscopical sections showed tuberculosis of the lungs, adrenal glands, and lymph nodes. The spleen was normal. There were only small islands of adrenal gland remaining (figure 1).

I found five other cases of Addison's disease in our files. The spleen was enlarged in four and small in one. The weights were 250, 320, 300, 600 and 80 gm.

"Draw your conclusions before your experience is large . . . Those of large experience are wary of conclusions."

Dr. Will Mayo, quote in Clapesattle's "The Doctors Mayo"

(Continued from page 8)

cells, occasional leukocytes, few fat globules, and numerous cholesterin crystals. No fungi or hooklets of Echinococcus could be demonstrated. A portion of the fluid was sent to the National Institute of Health Laboratory for a complement fixation test for Echinococcus, and reported negative. Histologic examination of the cyst wall showed a dense, fibrous tissue with areas of hyalinization. There was some inflammatory reaction in the outer two-thirds of the wall. No epithelial lining could be demonstrated. Hemorrhagic cyst of the spleen was the final diagnosis (figure 2).

SUMMARY

Two cases of splenic cysts of the false, hemorrhagic type are presented. Splenic cysts are relatively rare, the false hemorrhagic variety being most common. If the disease is considered, it is conceivable that a preoperative diagnosis can be made. The characteristic displacement of the left kidney downward, displacement downward of the splenic flexure of the colon, and displacement of the stomach to the right on barium meal are very suggestive of splenic cysts. These findings are usually associated with a palpable mass in the left upper quadrant which extends below the left costal margin and to the right. Experience here is that splenic enlargement due to other factors very rarely causes displacement of the kidney. No discussion of the treatment has been given as there is only one treatment and that is splenectomy. This is always indicated in large cysts of the spleen, but may not be necessary in very small cysts.

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(Continued from page 17)

is being given proper care. The patient's care may require the use of another medical facility such as a sanatorium, orthopedic hospital or convalescent home. In other instances, parents need help in working out educational plans for a handicapped child. Relatives are advised of the necessary procedures for having their child admitted to special education institutions. Patients with marital difficulties may need to be referred to family agencies for counseling.

Doctors may wish to know what the patient was like before illness or what bearing strains and pressures of the social situation may have on his illness. The social worker secures information through interviews with the patient, relatives, with the community agencies familiar with the situation. She is able to evaluate the information received as it pertains to the problem under study.

In helping patients carry out the doctor's recommendations and in solving the problems interfering with medical care, the social worker enters the field of preventive medicine, for with such help further medical complications are avoided. The medical social worker, in her continuous contacts with agencies and through discussions about patients, gives the local social worker knowledge of illness and disease, and an appreciation of the requirements of medical care.

In the course of her duties, the social worker becomes aware of gaps in community planning and the lack of specific resources which are needed, and so advises the proper authorities or planning boards so that eventually the situation can be corrected.

The social service department performs many public relations functions for the hospital or clinic. The medical social worker has contacts with relatives, interested persons, patients, community agencies, and groups. She explains policies and requirements of the administration and the methods and procedures of the medical staff to a large section of the public. In return, she learns of community conditions affecting the lives of patients, which she brings to the attention of the hospital administrator and the medical staff. In every hospital or clinic there are those patients who do not fit into the established routine procedures. There are likely to come to the attention of the social worker, so she is aware of the effect of the hospital's policies and procedures on patients. Since interpretation is an essential part of providing for the needs of patients, every social worker has a great number of contacts in a period of a year.

The medical social worker assists the doctor in his treatment of patients. The personal and environmental problems which interfere with the medical care of the patients are her concern. These being solved, the doctor is free to proceed with his plan for treatment. Medical social work facilitates medical care in its achievement of the goal of modern medical science, to take care of the sick and to help them make the maximum adjustment to life, commensurate with their ability.

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Medicine in Great Britain

Some Personal Experiences and Observations

JAMES ROGERS FOX, M.D.*
Minneapolis, Minnesota

I WAS FORTUNATE enough, as a result of an appointment to the staff of the University of Edinburgh, to spend the months from April through July observing hospitals, medical schools, health services and industrial medical centers throughout the European mainland and Ireland, but in particular in Great Britain. Although the majority of my observations, which I should like to point out as personal experience, occurred in Edinburgh, I did have the opportunity of observing quite thoroughly medical schools, health services and hospitals in Glasgow, Aberdeen, St. Andrews, and London, as well as industrial medical centers in Glasgow, Slough, and London. In addition, I participated in a postgraduate course of internal medicine at the University of Edinburgh and attended two medical conventions. The factor which best qualifies my writing with some authority on medicine in Great Britain is that I was a member of the British Medical Council Registry, and as such participated in socialized medicine as it is practiced in Britain.

First of all, I feel that general understanding of the European outlook on life is essential if one is to understand better their approach to medicine. The countries of Europe which we have all known in the past are far different today. Great Britain in general shows the most apathy in its attempt to come back. There were two general arguments for this that I heard time and again from one end of the island to the other. The first was that in the 1914-18 war the great majority of the young men who would have been the leaders of today were killed, and, as a result, a substantial leader group is lacking. Secondly, it was pointed out that Great Britain, although it had won the war, was in a difficult state. Had it lost the war as Germany had, there would have been a buckling down and an effort to come back in entirety. Conversely, if they had won the war handily, there would have been no difficulty in attempting to get back to normal living. However, they had been beaten over a period of years, to the extent of having less get-up-and-go than previously. Thus it was felt that a natural let-down following the war, superimposed upon the recent governmental administration, had caused the average "let John do it" attitude. However, many of the other countries which should be regressing have improved, and although the economic balance is precarious, the people themselves have advanced, as in the south of Ireland and in Belgium. Medicine in Britain is very much the same as medicine in the United States and yet in a way completely different. A good portion of this, as in other phases of British life, falls to the fact that tradition is more important than efficiency. There are many many exceptions to this in all directions as is usual in the distribution curve.

JAMES ROGERS FOX *is on the staff of the University of Minnesota Student Health Service and is assistant director of continuation medical education at the University of Minnesota medical school.*

*University of Minnesota Health Service.

MEDICAL EDUCATION

To begin with, medical education in Britain is considerably different from that in the United States. It is only recently that the course has been advanced from five to six years. A student applies for medical school immediately upon leaving what corresponds to our high school, at the age of 17 or 18. He can complete his education at 22 or 23, with the degree of B.M. (Bachelor of Medicine) and B.Ch. (Bachelor of Chirurgerie). He must then pass an examination corresponding to our National Board or State Board in order to obtain a license to practice. Until this year, had he so desired, he could have begun practice immediately upon leaving the university. The greatest percentage of graduates obtain one year of hospital training corresponding to our internship. Thus students complete six years of medicine in Britain as contrasted with an average of seven or eight in the United States.

Graduates as a whole seem better founded in basic sciences but less well founded in clinical medicine than those in the United States. As mentioned previously, a person may spend one to five years in the hospital. He may have clinical work and must write a thesis in order to receive an M.D. or a Doctor of Medicine degree. After five years of practice, he may "sit" his examination as a physician, in seeking membership in the Royal College of Physicians, or as a surgeon in the Royal College of Surgeons. It is not essential that this time be spent in hospitals. Most often persons seeking membership take a concentrated postgraduate course of about three months and thereafter "sit" membership in London, in Edinburgh or in Dublin. These are all separate societies with essentially the same recognition. A physician upon passing his examination becomes a member of the Royal College of Physicians and is proposed as a fellow after some time within the organization. The surgeon becomes a fellow of the Royal College of Surgeons immediately. Interestingly enough, the surgeons are called "Mister" and the physicians, "Doctor," a custom deriving from the days when surgeons were associated with barbers. There is often correction if the surgeon is inadvertently addressed as "Doctor," unless he also happens to have an M.D.

The postgraduate courses at Edinburgh were directed toward specialists or toward general physicians. A course for general physicians lasts two to four weeks and under the National Health Service Act a physician could leave his practice and be paid while attending a course of two weeks. This is one good factor arising from the National Health Service which should promote further training and keeping abreast of medical changes. In addition, there are those physicians who, desiring to sit their membership as specialists, take courses in internal medicine or surgery which last about three months. These courses consist of two to four lectures a day, together with discussion periods, clinical observation, and laboratory demonstrations. The materials presented are excellent, and although the scientific side of medicine is stressed, the art of medicine is even more so.

THE PRACTICE OF MEDICINE

One finds a marked difference between the general physician in Great Britain and in the United States. There he does not use a hospital, and for the most part there are few buildings which have concentrations of physicians. Instead the general physician has his office within his home. Occasionally, especially if he is in a larger city, he will be a member of the Royal College of Physicians and if so, is apt to have a higher paying clientele. He does a great deal of his work making house calls and seeing patients within their homes. Often he brings a nurse to the home, but there are many buildings which are set up as nursing homes and are used rather than hospitals by those with higher incomes.

Hospitals for the most part are ward in nature, although in a few instances, as in London, there may have been a paying wing, and therefore private care and private rooms. For years gone by—since the 1700's in Edinburgh—the hospitals have taken care of the poor, the indigent, and the emergencies. None of these people had to pay during their stay in the hospital, the economics of which I shall mention later. Since the hospitals were composed of wards, the persons with higher income preferred nursing homes, with adequate nurses, physicians and care. The difficulty here lay in facilities for laboratory procedures. The Royal College of Surgeons had a laboratory in Edinburgh which would take care of all the service a physician might need, but this has been abolished since the National Health Service. Portable x-rays could be brought in, or the patient could be transported to the x-rays, depending upon the situation. Surgery and obstetrics are performed in these nursing homes in excellent operating suites. Thus they can be compared with our private hospitals, although with less facilities.

The specialists are removed from the general physician in that they associate with hospitals for the most part and then see private patients in consultation. Thus they have facilities available at all times. Previously they had taken these positions without pay, merely for the honor; however, now they receive a governmental salary.

The art of medicine far exceeds any that we have here in the United States! This is true of nurses, technicians, etc., as well as physicians. In nursing, the students are selected more for their quiet cooperation, efficiency, rather than for extreme intelligence. The nurses are intelligent, but it is felt more important that they be excellent in the art, rather than the science of nursing. Their duties are quite different from those in the United States. Nurses do not take blood pressures; they handle all the bed pans, meals, and the like, and only in administrative positions is it necessary for them to have advanced degrees.

Hospitals are quite specialized in that there are orthopedic hospitals, childrens hospitals, obstetrical hospitals and the like, and within the Royal Infirmary of Edinburgh, each wing is a separate specialty within itself. The hospitals themselves are very slow in their turnover of patients. This is especially true in the gynecological group. In general, patients are discharged considerably later than they would be in the United States. This is true partly because of the poor home life of so many, but principally because the cost is not to them as it is here in the United States.

There was a waiting list of 1400 patients to get into the Royal Infirmary of Edinburgh which has approximately 1500 beds. Any emergency case is admitted immediately, but those brought in for diagnostic purposes, particularly in elective surgery and in certain fields, have to wait. However, all emergency care is available at all times.

The nurses' hours are considerably different within the hospital. There are split shifts and the night nurse is off at 8:30 a.m. rather than 7:00 a.m. as is usual in the United States. All patients are awakened with a cup of tea, which of course, takes considerable time, and breakfast comes later. This cup of tea at the bedside is the usual British habit and a very pleasant one.

The worst feature is the handling of tuberculosis. There are no special tuberculosis wards in many, or most of the hospitals. Nobody is anxious to give up his ward, or a portion of it, in order to isolate the tuberculosis cases. Thus, an open case can stay in a ward over a period of time. This is not because the tuberculosis authorities have not attempted to correct matters, but because the cooperation is not what it should be.

UNIVERSITY STUDENT HEALTH SERVICES

During the stay in Britain, I had the opportunity of directing the health service at the University of Edinburgh, and of watching and studying health services of other universities throughout Britain. In general the health services are relatively small as compared with those of the American universities. Some of the health services are excellent, but there are as many types as there are universities. Some of them use the registry in which the student becomes a part of the register of the physician at the health service. There are others in which this registry is not utilized. This of course makes for difficulty in administration and care of the student. There are the same problems in cooperation that we have here in the United States, and in a good many instances it is difficult to even get a routine chest x-ray in an attempt to control and protect students from tuberculosis. This is hard to rationalize in the face of compulsory medicine throughout the state of Great Britain and the fact that the set curriculi of various colleges are never questioned.

Of all the health services that I did see, there was a very definite progress (with but one exception) toward the adequate care of students, but above all toward the education and cooperation of students. In general the students seemed quite pleased with the care given them and in Edinburgh, where I came to know many of them well, I noted a genuine interest in medical care. Some of the universities also have the social service office. In Edinburgh this was adjacent to the health service, a situation which was of considerable value to students in placement in adequate homes or "digs" as they were called, and in adjustment to university life. In general, health services in universities in Britain are progressing but still have a great way to go. In some instances the National Health Service has impeded this progress and in others it seems to have aided.

EFFECTS OF THE NATIONAL HEALTH SERVICE

We must consider again the fact that the general physician works in the private home, not in the hospital, and that the hospital is of the ward type. The hospital staff is comprised of specialists in the various fields. In so far as the payment of the physician was concerned, preceding the National Health Service Act, a pa-

tient paid according to his means. The scale was a sliding scale, and of course there were abuses there just as there have been here, and just as one notes in the National Health Service scheme today. At present, the physician is permitted to have four thousand persons at the most as patients on his registry, and he is given $2.38 per year per head. All of this is before income tax. A specialist is able to get more than this since he may have a certain number of referrals per year which will add to his income. In addition, he is on a hospital staff and is given a set salary.

Support of hospitals

In so far as the support of the hospital is concerned, preceding the National Health Service Plan nearly every community in Great Britain had an infirmary. The larger the community, the greater the infirmary and in some instances there was more than one. These hospitals were maintained entirely on a voluntary basis and it is interesting to see today, painted on the walls, names and dates going as far back as the 1700's, of those who have subscribed certain amounts to the hospital, and to note that these people came from all walks of life and all parts of the world. There was a great deal of pride in this maintenance and care was considered outstanding.

Since the socialization plan, the government runs the hospitals from the standpoint of finance and of course, hardly anyone is donating unless it happens to fit into his income tax scheme. This pride that I mentioned has been replaced with a considerable amount of apathy and of petty jealousies. This is not on an obvious plane, but when one works a period of time in the area, it becomes more evident. In addition, the hospitals themselves are more run down, just as the railway stations throughout Britain. Newer equipment and painting are needed, and in talking with the administrators of several of the hospitals, I found that they were generally agreed that the hospitals are going down hill.

The National Health Service took no account of the nursing homes, and they are not considered at all. Previously, insurance plans, just as we have here for our private hospitals, and personal payments kept up the nursing homes. That too is true at the present time. The greatest proportion of the physicians whom I had come to know, carried insurance schemes for their own families in order that, should they require hospitalization, they might receive nice rooms in an adequate nursing home. This of course was stimulated by the fact that there is such a waiting list to get into hospitals as well as by the fact that the hospitals are of the ward plan.

Distribution of funds

The cost of the National Health Service scheme was estimated by their government to be 170 million pounds. Last year the expenditure was 450 million pounds and an expenditure of 510 million pounds is anticipated this year. As I mentioned, hospitals are run down for the most part, but private enterprise in the form of the Red Cross is showing the way. I visited two hospitals run by them that were outstanding. Certain medications are under central control. If an individual desires some aureomycin, for example, he has to give the diagnosis and submit it to a central area. This would prove a good plan, as would so many others on paper, except for the fact that here again individual weakness makes for personal preferences. This too is true of beds, in so far as central controls are concerned. The medical schools are receiving support money also, to be used for the expansion of medical education. The dean of the medical school told me that they are given a free hand, but are beginning to be questioned as to where they are using the money, and in what manner. He believed that the next step conceivably would be the direction, by the government, of the use of the funds for each of the schools.

Medical care

Just what effect on medical care all this has brought about is far reaching. First of all, one must recognize that these patients do not get all of this for nothing, but rather a certain amount of money paid by each individual who is compelled to join the plan, pays for a part of the care. Taxation is added to this. Certainly the overwhelming cost of the program as quoted above, points out that there is considerable load placed upon the country as a whole, for many services unnecessary at present. It would have been far more expedient to have used the greatest portion of this money for housing and food, which are more important to life. Immediately after the war, when it was planned to increase the scope of the medical plan, which had been in use in Britain since 1911, the whole thing became a political football, at a time when essentials were more necessary.

Health Service care is not abused by all, of course, but by sufficient to make life uncomfortable. For example, when George VI died, two physicians in Edinburgh told me that they

had the busiest single day they had had in over twenty-five years of practice, since pubs were closed, movies were closed, and the people went to the doctors offices. They finished the day at 11:30 p.m.

The abuse of glasses, prostheses, drugs and the like was so severe as to cause some changes to be made. Now the person seeking glasses must be examined by his physician, which merely throws more of a burden on the general physician who then refers him to an optometrist or to an oculist. In so far as drugs are concerned, a charge of 14 cents per prescription, no matter what it is, is made. Of course, some people object because a drug for which they normally paid 10 cents now costs 14 cents, forgetting that certain of the more expensive drugs, such as aureomycin which would run into many dollars, also cost only 14 cents. The nuisance charge for prescriptions has not done too much, although it had been in effect but a short while before I left Britain.

The physicians are somewhat taken back by the fact that if they receive a call from a member of their registry in the middle of the night and do not consider it necessary to go to him, they may be reported to a board composed of lay persons only. For the most part the patient is glad to accept the physician's opinion, but if he should be unhappy about the decision, the physician is responsible to the lay board.

Probably the biggest single effect of National Health Service is the ratio of patients to physician. As we are all aware, a general physician cannot adequately take care of more than 1500 to 2,000 patients. Generally the physician who spends more time doing an adequate job will see less patients. Those who, as general physicians, are extremely rapid, may possibly do less of a good job. In other words, there is just so much time in a day, and if a physician is to give adequate care to his patients he cannot take a larger load. But what has happened in Britain is that the greatest number of physicians now, for reasons of livelihood, must necessarily have their 4,000 registry. Those who want to continue practicing the brand of medicine they have been practicing, find their registry will be less and therefore, their income less. In other words, the conscientious physician gets less money and the physician who sees many patients gets more money, the charge being on the basis of number rather than on quality. Here in the United States, as it used to be in Britain, a physician with a reputation for a thorough, all-inclusive job, will receive referrals, can see patients for a longer period of time, can give a more thorough examination and care, and receive adequate recompense.

In years gone by doctors were given their appointments as an honor, which did help their referral work, but now they are on a salary basis and get a certain amount of added income for referrals. Although it is not true in all instances I was told that there is more jealousy among various departments and physicians in the hospitals than there was before socialization. Whether this can be attributed to the National Health Service, I do not care to guess.

In so far as industrial medicine is concerned, there was an upsweep of medical care for a number of years. However, now, it is being diminished from the standpoint of persons running industrial medical centers, because industry is already overwhelmingly taxed to care for its workers. For many years there has been a safety engineer (from the time of Victoria) who would examine the various factories and to whom management was accountable. If anything should go wrong because of laxity, he, as a government representative, could close the factory. Pre-employment examinations and pre-employment x-rays are on the increase, but not required, and the centralization of industrial medicine throughout the whole of Britain has been waning since the advent of the National Health Act, for the reason mentioned previously. The effect of health service in the matter of tuberculosis care has been nowhere near what one should have anticipated. Actually the major medical problem in Great Britain is that of tuberculosis. A fraction of the money used for the National Health Service, if used for setting up an adequate tuberculosis control in the form of isolation and treatment, would have done far more for the actual health problem. There are 50,000 empty beds in scattered small towns in Britain, a result of the dispersing plan during the war. The problem of tuberculosis could be helped immeasurably by using these, for there is a several month wait for admission to other sanatoria. The main reason for not using them is the lack of staff; however, with sufficient monetary and social inducement, staff could certainly be recruited. This one project and expenditure would have had a marked effect on Britains health.

Background of socialized medicine

Actually, socialized medicine in Britain began in 1911. Before the advent of this National Health Service Act there was a registry of all those persons who earned under 400 pounds a

year, in those days amounting to about $2,000. Thus low-income persons were cared for, and the rich could afford care, but the argument was proposed that those persons corresponding to our salaried personnel in the United States were caught in the middle. However, in those days, they would carry insurance and go to the nursing homes, and now they are in the wards and often on a waiting list to be admitted.

Attitude of the British toward the National Health Service

What is the attitude of the British? I had the opportunity of talking to well over 150 physicians briefly, and with 66 at length during my stay in Great Britain. Of these 66, who were a cross section of the various areas of the country, I did not find one who likes the National Health Service as it is now in effect. Nearly all felt that it was well to have a Health Service Plan, and that broader scope of care is necessary. They all agreed that the threatened blast of thunder that occurred was wrong. Each said that the British Medical Association had let down the physicians. This all apparently stemmed from the fact the officers in the British Medical Association stimulated various meetings in an effort to combat this possibility but suddenly, starting from the top and going on down, they all began to decide they would take the socialized plan rather than be left out in the cold.

I had the opportunity of meeting several physicians who would not join the plan and who have continued to go on with a very adequate livelihood—thus the fear of being left was not necessary. Talking with the physicians as to how their problem might have been resolved, I find that it comes to the same thing that we have here in the United States. They feel they should not have been negative in their approach, but rather should have set up earlier a definite plan which was acceptable, far less expensive, and proposed it before the group who enforced the legislation had the opportunity.

It is impossible to compare Great Britain with the United States in any way. Tradition, attitude, government, size, and production, are all different. The one analogous lesson which is quite evident is that we should set up a plan and have it ready as soon as possible.

Interestingly enough, all the socialization factors in Britain show no apparent progress. Railroads are in horrible shape, medical care, as I mentioned, certainly is not what it should be, the roadway system which was set up for truck transportation, proved to be more expensive than it was under private enterprise. One can go on indefinitely with the pros and cons. General physicians, with the exception of those who practice in the industrial areas, are not pleased with the situation. The latter are seeing about as many patients now as they ever did, but are being paid $2.38 per head, and have an increased income. However, many of the industrial physicians do not like the way it is done. Lay persons on the other hand, are just as we would have here in the United States. The white collar worker is not very pleased with it, as he likes to have his head up, and does not like to be "given something for nothing." The farmers, particularly those in the northern areas, are against it. Laborers are both pro and con—those who recognize it is killing off their government do not like it. The unskilled laborers, for the most part, are all for the fact that they are getting something that they had not received from private physicians before. When this is discussed, the answer is always "we can tax the rich people," or "the government will pay for it." In the upper income bracket a man is permitted to keep 7 cents out of $2.80 that he may earn, so there is no further taxation possible. Those who were highly wealthy are quickly being reduced.

BRITISH MEDICAL ASSOCIATION

We had the opportunity of attending the meeting of the British Medical Association and the Irish Medical Association in Dublin. To begin with, we went as a guest to the representatives' meeting, where we listened to the election of officers and the commendations of those persons who had been in special service. Then we listened to a number of the various questions to be presented before the meeting. It was not unlike attending Parliament, Congress, or the A.M.A. meeting. There were as many scenes of farce as there were of intelligence.

I was quite impressed by the fact that from the committee it was determined that the selection of the city for the meeting of the British Medical Association henceforth would be decided by the officers of the association rather than by acceptance of an invitation by a given city during a meeting. This was worded in such a way as to be a directive rather than a request. One physician rose and in a spell of eloquence pointed out that there had been sufficient centralization thrust upon them over the last few years, that no matter what the argument would be about the size of the city, hotel facilities, etc., it was not for a few to decide where the meet-

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The Role of Anxiety in the Physician-Patient Relationship

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PHYSICIANS and laymen alike have long recognized the crucial importance of the relationship between patient and physician. Patients are individuals, and differ in the characteristics they seek in their physicians. Physicians are also individuals, and differ in the qualities they are able to display to their parents. Necessarily, then, details of the personality interaction in the professional situation can be almost infinitely varied.

One of the most important of the many factors which influence the physician-patient relationship is the anxiety of the patient. Rickman[1] and Stevenson[2] are among the many authors who have touched on some aspects of this problem. Unfortunately, however, this factor has been too often ignored, and no systematic formulation of the function of anxiety has appeared heretofore.

The term "anxiety" as it will be used in this discussion refers to "diffuse, undifferentiated apprehension," "uncertainty and helplessness in the face of danger."[3] The term will usually be applied to feelings arising from circumstances centering around acute or chronic illness. There are, of course, important sources of anxiety other than illness, and when anxiety on the basis of one of these other factors is mentioned, the change in the referent will be made clear.

The first function of anxiety in the physician-patient relationship is that of driving the patient to seek medical attention. He may of course seek relief from any of hundreds of conditions which are distressing or unsatisfactory for reasons other than the anxiety they may arouse. Pain is an obvious example. Disfiguring skin lesions are another, as are congenital anomalies, tinnitus, pruritus, myopia, and a long list of others. As soon as a patient with such a problem becomes aware of it he may decide that it is sufficiently irritating to warrant medical attention. He arranges to secure such attention within an interval which may be largely determined by the severity of the symptoms. Severe pain may demand an emergency night call, while consultation about the removal of a keloid is arranged in more leisurely fashion to suit the greatest convenience of the patient and the physician. Yet probably more often than not, this "rational" or "common sense" approach is not followed.

Every physician has seen patients who have had pain, for example, for a long time before seeking medical attention. Exacerbation of the pain is not necessarily the cause of the patient's coming to his physician—in fact, the history will often reveal that the pain has recently decreased. The patient's reaction to his pain and his evaluation of it have changed and this change has motivated his visit. It may suddenly have occurred to him that his pain might be caused by a cancer, and the fear of such a threat to life sends him seeking help. The patient may have had a degree of anxiety insufficient to make him seek medical aid, then other circumstances arose to generate other anxieties — financial difficulties, family disputes, etc.—and the total burden of anxiety became intolerable. He now seeks to reduce the anxiety arising from his longstanding physical ailment, thus making it possible for him to bear his other troubles. This may help explain why for so many patients it never rains but it pours, and hospitalization for treatment of old ailments complicates many a family crisis.

It is banal to say that there is great variation in the calmness and good humor with which patients bear anxieties resulting from what seem to be their physical ailments. Too often physicians, nurses, and relatives tend to be intolerant or contemptuous of the patient's reaction to a given illness. These evaluations of his behavior are not likely to produce a sympathetic understanding of his problems nor serve as an effective therapy for any of them. The physician needs to keep reminding himself — and often others as well — that there are constant fluctuations in the total anxiety level of the patient, in the relative

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importance of different causes of his anxieties, and in his ability to cope with them.

Interns are often amazed, when they are not exasperated, by patients who come to a hospital emergency room at two o'clock in the morning for treatment of an illness which has been present for many days or weeks. This rather common occurrence is best understood in the light of the patient's anxiety. It is generally accepted, though there may be no objective proof of it, that people tend to worry more at night. The myriad distractions of the day are all but gone. Others are asleep, but the sleepless patient tends to ruminate on his troubles and to magnify them. When his anxiety mounts to a critical point, he gets out of his bed and wakes a doctor.

A second function of anxiety in the physician-patient relationship is directly opposed to the first—it may keep the patient from seeking medical attention. If the patient feels sufficiently threatened by what he thinks he will be told, he may go to almost any lengths to avoid medical consultation. Cancer, heart disease, tuberculosis are examples of ailments which patients fear to learn they have. The emphasis in the current national campaign against cancer is that it is often curable when detected early enough. This has lowered the anxiety in many patients so that they have been willing to consult their physician fairly soon after noting symptoms. Other patients feel threatened not so much by cancer as by the surgery that is necessary to extirpate it, and postpone treatment until too late. Anxiety may be focused on other forms of treatment or examination — gynecologic, endoscopic, etc. No one is more familiar with such anxiety and its effects than the dentist.

Third, anxiety functions as a major determinant in the patient's choice of physician. Given any sort of choice, the patient tends to choose the physician who is most successful in relieving his anxiety. It is perhaps worth saying again that no claim is being made that this is the only important factor. There are various reasons that a patient goes to a given physician in preference to others. However, the physician will fail to appreciate many significant aspects of his relation to his patient if he neglects the function of anxiety.

The most important task of the physician, so far as the patient is concerned, is the reduction of anxiety to a tolerable level. Consider, for example, those patients with chronic illnesses which are not greatly improved by any method of treatment. The patient knows that his ailment is incurable and that he simply has to live with it. Why then does he return over a period of years to a man who he knows cannot heal his physical infirmity? It seems the answer in most cases is that the infirmity as such is far less important than the patient's evaluation of it. He considers it a threat to life, or at least to comfort and well-being, and the anxiety aroused by the threat must be repeatedly allayed. If the physician is successful in treating the anxiety, the patient keeps coming back. If he is not, the patient goes elsewhere, and keeps going from one doctor to another until he finds one who is able to keep his anxiety down to a bearable level. In many instances the patient's anxiety is so great — for whatever reason — that no one can keep it within bounds. These unfortunates are driven to seek one physician after another, and in addition usually turn to non-medical forms of treatment.

Other patients suffer from illnesses which are self-limited, and from which they will recover with almost any form of therapy or with none. Yet knowing this, many such patients present themselves for medical attention. Clearly their "rational" evaluation of need for treatment is of less importance than other factors, not the least of which is anxiety. They know what they are going to be told, but they come to listen to it because their anxiety demands that they do.

What must the physician do to relieve his patient's anxiety? Any attempt to answer this question with a set of general rules would be ridiculous. It would seem legitimate, however, to point out various forms of behavior which seem importantly related to the reduction of anxiety in certain patients.

One of the important techniques for reduction of anxiety is sympathetic listening to the patient's story. Probably most persons respond positively to such behavior. Taking a careful history forms part but not all of this listening. Medical training has stressed the importance of a good history to the doctor, but has not sufficiently stressed its importance to the patient. It is easy to consider a patient tiresome or egotistical who gives an elaborate history full of irrelevant detail. Such an opinion may be partially correct, but more important is the patient's desperate desire to feel that he is understood. Less often the taking of a detailed history increases anxiety by suggesting that there is significance to symptoms previously ignored.

For many patients the highest word of praise for a physician is that he is "thorough," by which they usually mean that he takes a detailed history, does what they regard as a careful physical examination, and orders many laboratory

and x-ray studies. Other patients are irritated by anything they regard as unrelated to what is the matter with them, and they demand that the doctor at once get to the business of prescribing a cure. The anxieties and prejudices of both sorts of patients may result in modifying what the physician might otherwise do.

Most patients would like to find in their physician a pleasing personality, even though there might be little agreement on which personalities were pleasing. A large number of patients, however, are in need of an authoritative father-figure, a stern autocrat who will give them orders rather than advice. Others can find the reassurance that relieves their anxiety only in the international reputation of a great specialist, and are little affected by his actual behavior. Some want logical reasons for every suggestion the doctor makes, while others are made more anxious by any attempt at explanation.

While no physician can be all things to all patients, every doctor modifies his behavior, even though unconsciously, to suit the needs of the patient so far as these are obvious. By what he does and what he does not do, the successful doctor gives his patient the feeling that he understands his problems, that he takes them seriously, and that he is competent to deal with the situation. Even the most inept physician has successfully reduced the anxieties of some of his patients, and even the most brilliant cannot succeed with all.

The fourth function of anxiety in the physician-patient relationship is that of motivating the patient to carry out his share of the treatment. Medications which are prescribed must be taken regularly, braces must be worn after they are fitted, diets must be adhered to. Only the relatively small fraction of patients who are hospitalized can be supervised regarding these matters, and even these patients must usually give at least a minimum of cooperation. It is erroneous to assume that all, or even most, patients will automatically carry out advice regarding medication, diet, etc. In most instances, as soon as the patient's uneasiness has declined to a tolerable level, he forgets to take his medicine, or decides that wearing the brace is too much trouble. It is a general and a wise practice of physicians to prescribe drugs in amounts sufficient to last only until the patient's next appointment. When the patient returns and is given a prescription for more medication, he will often proudly assure the doctor that he has plenty of tablets left for another two weeks. The half-filled bottles in the family medicine cabinets of the nation are eloquent proof of the relief of their owners' anxieties. The thousands of appointments cancelled every day would be kept by people whose anxieties were unrelieved. Thus patients whose level of concern is particularly labile may neglect important ailments, and their decreased concern makes it all too easy for the busy physician to neglect them.

In the case of the pediatrician it is not so much the disquiet and uneasiness of the patient as those of the child's parents that are the determining factors. It is the parents who decide that their child needs medical attention, and the parents who select the child's physician. If their anxiety remains high they may wander from one doctor to another. If the first doctor succeeds in reducing the parents' concern, they will probably stick with him. Obviously it is necessary for the physician to pay particular attention to keeping the parents' anxieties within comfortable bounds, for the child's sake as well as the parents'. But the child's anxieties deserve more consideration than they sometimes get. Because he does not know what to expect in even the simplest clinical situation, the child often replaces his painful uncertainty with equally painful fantasies. Frequent reassurance by means of explanations as complete as the child can comprehend will prevent many difficulties for the pediatric patient.

Nearly always it is the parents rather than the child who carry out prescribed treatment or fail to do so. Even older children usually need to be reminded to take medications, and with infants and young children the entire burden falls on the parents. The child usually receives medications regularly as long as his fever lasts, but often only haphazardly therafter. Frequently the parents are concerned about only one aspect of the child's problems, and when reassured on this point they stop bringing the child for further attention. For example, a three year old boy was seen because he had no speech. The history disclosed several important environmental and psychologic reasons for this retardation, but before a definite diagnosis could be made, tests of hearing and intelligence were carried out. The parents interpreted certain remarks of the clinical psychologist to mean that the boy had better than average intelligence. (Actually he was average.) They refused to return for discussion and suggestions for therapy, for, they said, they had been worried only as to whether the child was mentally retarded. Over a year later the adverse influences in the environment remained uncorrected, and the boy's speech was still

markedly retarded. Practice with adults as well as with children may be complicated by such a tendency to focus all the anixety on one aspect of a many-sided problem.

Additional evidence for the pervasive influence of the patient's anxiety in his relationship to his physician can be found in many of the seemingly trivial aspects of this relationship. Even the patient's words as he greets his physician or says goodby reveal his concern. One of the commonest ways of reducing anxiety, at least temporarily, is the use of humor. The grim jokes of the battlefield are an excellent example. The dramatist usually finds it necessary to provide comic relief in the sweep of his tragedy. The very term, "comic relief," designates precisely the function that humor has for all of us in situations of uneasy tension. So too the worried patient jokes with his doctor about his illness. His jokes tend to be stereotyped, and may even become tiresome to the doctor who does not realize their real function. The doctor asks, "What's the matter with you?", and grinds his teeth when he hears for the hundredth time, "That's what I came to you to find out." He finishes a physical examination of a patient with a relatively minor illness, and finds the man grinning at him with, "Well, doc, do you think I'll live?" When the patient is really seriously worried about his chance of surviving, it is usually too painful to him to verbalize his concern. These and other clichés are repeated by so many patients because the situation which evokes them is so often repeated.

The pediatric patient must often be given immunizations or other injections causing pain. The child's crying arouses anxiety in the parent, and this is often relieved by similar attempts at humor. It is common to see a mother laughing as she dresses her crying youngster after a "shot," thought there is clearly nothing funny in the situation.

Every physician has seen something of the way in which his patients' anxieties have modified their behavior. Much that has been discussed herein will have a familiar ring. It would seem important, however, to systematize the everyday clinical observations that most physicians have made.

Throughout this discussion many statements have been made as if the patient's anxiety arising from the threatening circumstances of his illness were the only important factor in the specialized relationship between two human beings, one a physician and the other his patient. Such exaggeration is necessary for the sake of emphasis, but it is well to repeat what was said at the outset. There are many factors of significance that shape the relation between physician and patient, and the role of anxiety has seldom been explicitly recognized. Continuing awareness of the importance of this role will help the physician to serve his patients better.

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Disruptions of normal function of enzyme metabolism may be caused by alterations in the flow of hormones from the pituitary, adrenals, thyroid, or pancreas. Abnormalities in the oxidation and storage of glucose and glycogen follow and ultimately result in diabetes.

There is accumulating evidence establishing the importance of hyperglycemia as a cause of diabetes. In order to prevent or delay the onset of diabetes, the insulin-producing cells should be allowed to rest. Prevention or control of hyperglycemia by diet, adequate insulin dosage, and avoidance of all known hyperglycemic factors, is highly important.

The pancreatic beta cells are abnormal in 87 per cent of diabetic patients, and the average insulin content of the pancreas is 25 per cent of normal, approximately 50 units per pancreas. Even histologically normal-appearing beta cells may be functionally inadequate, however, because of inefficiency, fatigue from overwork, and toxic effects. Hypoglycemia, induced by excess insulin, and continued for three to eight months, will produce low insulin content in the pancreas. A long-continued high-fat diet, particularly with excessive animal fats, causes degranulation of beta cells.

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A Controlled Clinical Evaluation of Two Hematinic Agents

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THE recognized usefulness of iron for the purpose of stimulating hemoglobin formation is based on established physiological principles.[1] However, the employment of simple inorganic iron salts for this purpose often elicits undesirable side-reactions,[2,3] and iron salts of organic acids such as ferric ammonium citrate are often poorly utilized.[4]

Two research approaches to the total problem have long been pursued. One involves the discovery of an iron compound which might be both effective and well-tolerated. The other involves the concomitant use of auxiliary agents such as vitamins and certain inorganic compounds which may possibly enhance hematinic action. The unsettled state of opinion with respect to the value of these latter agents is fully recognized;[5,6] but from a practical viewpoint it must be remembered that they are widely used in the treatment of borderline anemias and associated conditions even though their quantitative worth has yet to be fully established.

The main purpose of this investigation* was to compare the therapeutic effectiveness and tolerance of a new iron compound, iron sodium malate, in combination with certain adjuvant substances, with ferrous sulfate. The latter was chosen as the reference medication because of its popularity and recognized physiological utilization.[7] Each medication was administered orally in the form of tablets containing the equivalent of 50 mg. elemental iron per tablet. Dosage throughout was two tablets three times daily; this schedule was employed because of previous clinical findings indicating that a daily intake of the equivalent of 300 mg. of elemental iron was optimal for the medication under study.[8] Neither medication was enteric coated.

Criteria upon which conclusions were based were both objective and subjective. Precise hemoglobin determinations at regular intervals were employed to measure relative effectiveness. Reports of favorable and unfavorable side effects were used to estimated relative tolerance.

Iron sodium malate is a new complex salt of iron. Its iron content is relatively high; e.g., 25 per cent in contrast to 20 per cent for ferrous sulfate, 18 per cent for ferric ammonium citrate, and 12 per cent for ferrous gluconate.[9] Iron sodium malate contains iron in both the ferrous and ferric states. It is readily soluble in water and gastric juice, and considerable alkali can be added to its aqueous solution before permanent precipitation occurs. This latter feature may be therapeutically significant in that it indicates that the iron may remain in a soluble form throughout a greater length of the gastrointestinal tract, thus permitting greater iron absorption.[10]

The preparations used in this clinical study were: (a) ferrous sulfate tablets, each tablet containing 250 mg. of $FeSO_4:7H_20$; and (b) Compound Iron Sodium Malate tablets (hereinafter referred to as I.S.M.), each tablet containing 200 mg. of iron sodium malate in association with 4 mg. copper sulfate, 200 mg. desiccated liver, 0.17 mg. thiamine hydrochloride, 67 U.S.P. units vitamin D, and vitamin B_{12} activity equivalent to one mcg. vitamin B_{12}. Each tablet of both medications supplied the equivalent of 50 mg. elemental iron.

THE CLINICAL APPROACH

In investigations of this kind, the customary approach has been to select patients having about 50 per cent normal hemoglobin levels and then follow the rate of hemoglobin increase un-

*Medications for this study were supplied by Reed and Carnrick, Jersey City, New Jersey.

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der medication. From a practical viewpoint this approach is unrealistic and the results are misleading for the obvious reason that such patients are not truly representative of those for whom oral iron therapy is intended because (a) they are usually non-ambulatory and require adjunctive medication, (b) the rate of hemoglobin increase is exaggerated because of the low initial level,[4,11] and (c) hemoglobin levels of such low orders usually represent rapid blood loss; the labile stores of iron are not depleted and their effect is not measurable.[12]

Because of its greater practical value, therefore, the approach employed in this investigation has been to utilize only those patients for whom this type of medication is commonly the only one prescribed—namely, those whose initial hemoglobin levels were from about 75 to 80 per cent of normal and who were not suffering from a macrocytic anemia or any other ailment which might render them refractory to oral iron therapy. They were in sufficient number and sufficiently accurately controlled so that significant statistical differences could be measured.

MEASUREMENTS AND OBSERVATIONS

Photoelectric measurements of hemoglobin levels were made at nine day intervals throughout the total test period. The resulting data were then subjected to statistical analysis to reveal significant differences in magnitude and onset time of therapeutic response and to evaluate periods of lag and acceleration.

With the institutionalized patients, red blood cell counts and hematocrits were determined before and after the test period in an attempt to measure relative hematological effectiveness with greater precision. These data will appear in a future publication.

Favorable side-effects were increase in appetite, improved sense of well-being, and improvements in general appearance (especially important in children). Constipation, diarrhea, nausea and other manifestations of gastrointestinal disturbances were regarded as revelations of patient intolerance. Satisfactory therapeusis demands relative freedom from such reactions.

TEST AND CONTROL PATIENTS

Three different population groups of test patients were included in this study which involved a total of 265 patients selected from approximately 1200.

The first group consisted of 66 women in the last trimester of pregnancy. All were out-patients of the Cambridge City Hospital, Cambridge, Massachusetts. In view of the recognized need for iron in this group,[13,14] controls were deemed undesirable because of the adverse effect the lack of iron might exert on the patients. Approximately half of the expectant mothers received ferrous sulfate while the others received I.S.M. Red blood cell counts and hematocrits were run to rule out macrocytic anemias. The study extended over a period of six weeks, measurements being made at nine day intervals.

The second group consisted of 103 carefully selected geriatric patients some of whom were general custodial cases while others were confined for chronic disease at the Long Island Hospital, Boston, Massachusetts. Patients selected represented the lower hemoglobin levels (75 to 80 per cent of normal) of the 933 tested and who seemed sufficiently cooperative and reliable to participate in the study. In general, there is a relatively high incidence of macrocytic anemias among old people; to eliminate these, initial red blood cell counts and hematocrits were essential. Four patients were subsequently dropped from this group because of persistent blood loss. This group was divided into three approximately equal parts. One part received ferrous sulfate, another part received I.S.M., and the third part received no medication. Measurements were made at nine day intervals over a period of six weeks.

The third group consisted of school children ages six to nine of Saint Catherine's School at Charlestown, Massachusetts. Sexes were equally represented. Random sampling was secured through alphabetical listing of names by grades.

The much greater prevalence of anemia in the juvenile and prenatal groups over the institutionalized geriatric group was very evident. This was especially true in the juvenile group wherein 80 per cent of those tested revealed hemoglobin levels on the order of 75 to 80 per cent whereas only slightly more than 10 per cent of the geriatrics were of the same order. Statistically, 933 geriatric cases were tested to procure 126 patients with hemoglobin levels within the above range whereas only 130 cases were required to accumulate 105 similar patients in the juvenile group. Although the food allowance in the chronic disease institution is low, it is apparently adequate without supplemental iron, whereas where dietary choice is limited by income, anemia tends to occur. This dietary factor enhances the preexisting tendency to anemia in the growth and pregnancy periods.[14] The importance of adjuvant dietary factors other than those supplied by the Federal Milk Program in primary schools is suggested in the low income groups.

TABLE I. All Patients

	First Week			Second Week			Third Week			Fourth Week			Fifth Week			Sixth Week		
	Mean[1]	N[2]	S.D.[3]	Mean[1]	N[2]	S.D.[3]	Mean[1]	N[2]	S.D.[3]	Mean[1]	N[2]	S.D.[3]	Mean[1]	N[2]	S.D.[3]	Mean[1]	N[2]	S.D.[3]
Control	12.11	71	0.81	12.14	70	0.77	12.11	69	0.79	12.12	70	0.75						
Ferrous Sulfate	11.95	102	0.87	12.10	99	0.81	12.25	102	0.77	12.44	102	0.79						
I.S.M.	12.13	92	0.90	12.43	87	0.87	12.65	90	0.82	12.93	91	0.83						
		265			256			261			263							
TABLE II. Prenatal Patients																		
Ferrous Sulfate	11.76	35	0.97	11.86	35	0.95	11.96	35	0.93	12.05	35	0.91	12.12	35	0.93	12.25	35	0.86
I.S.M.	12.01	31	1.17	12.53	31	1.16	12.61	31	1.13	12.70	31	1.11	12.80	31	1.09	12.95	31	1.03
		66			66			66			66			66			66	
TABLE III. Geriatric Patients																		
Control	11.95	42	0.65	11.97	42	0.61	11.96	42	0.64	12.00	42	0.64	11.99	35	0.66	12.03	35	0.55
Ferrous Sulfate	11.93	35	0.71	12.24	35	0.65	12.36	35	0.60	12.46	35	0.57	12.63	33	0.55	13.29	29	0.68
I.S.M.	12.13	26	0.71	12.33	26	0.65	12.55	26	0.59	12.74	26	0.60	12.89	25	0.64	13.30	21	0.86
		103			103			103			103			93			85	
TABLE IV. Juvenile Patients																		
Control	12.33	29	0.95	12.41	28	0.90	12.33	27	0.92	12.29	28	0.87						
Ferrous Sulfate	12.16	32	0.77	12.22	29	0.72	12.43	32	0.61	12.86	32	0.64						
I.S.M.	12.23	35	0.72	12.42	30	0.66	12.78	33	0.58	13.29	34	0.49						
		96			87			92			94							

[1] Mean hemoglobin concentration in Gm. per 100 cc.
[2] Number of patients.
[3] Standard deviation.

TABLE V. Critical Ratios—All Patients

Between Tests	1 and 2	1 and 3	1 and 4	1 and 5	1 and 6
Control	0.28	0.02	0.22		
Ferrous Sulfate	1.23	2.58	4.22		
I.S.M.	2.28	4.09	6.23		
TABLE VI. Prenatal Patients					
Ferrous Sulfate	0.39	0.87	1.25	1.56	2.18
I.S.M.	1.72	2.03	2.34	2.70	3.29
TABLE VII. Geriatric Patients					
Control	0.14	0.10	0.33	0.29	0.60
Ferrous Sulfate	1.87	2.69	3.39	4.47	7.70
I.S.M.	0.47	2.26	3.24	3.93	4.86
TABLE VIII. Juvenile Patients					
Control	0.30	0.08	0.16		
Ferrous Sulfate	0.27	1.52	3.84		
I.S.M.	1.12	3.41	7.05		

There were 96 children in the juvenile group. Approximately one-third of these received ferrous sulfate, another third received iron sodium malate, and the remainder received no medication. All patients were tested at nine day intervals over a period of four weeks.

Patients included in the total study are tabulated as follows:

Population Group	Number of Patients			
	Total	Receiving I.S.M.	Receiving Ferrous Sulfate	Controls
Prenatal	66	31	35	None
Geriatric	103	26	35	42
Juvenile	96	35	32	29
Totals	265	92	102	71

DATA INVOLVED IN THIS STUDY

Initial hemoglobin determinations were made on all patients. Measurements were photoelectrometric. Subsequent determinations were made after nine day intervals of medication, three on the juvenile group and five on each of the adult groups. Thus the study extended in the juvenile group over approximately four weeks and in the adult groups over approximately six weeks.

Red cell counts and hematocrits were made prior to medication on all adult patients and also at the conclusion of the test on all who had been institutionalized throughout the test period.

Data concerning side-effects were procured in the juvenile group through questionnaires sent to the parents at periodic intervals. In the adult groups, such data were secured through the observations of the nurses and the subjective statements of the patients.

After compilation by technicians and physicians, all data were then subjected to critical statistical analysis.

PRESENTATION OF DATA

Data relating to hemoglobin changes are presented both numerically and graphically in tables I to IV and in graphs I to IV. Tables and graphs are related; i.e., table I is related to graph I, and so on.

In addition to mean hemoglobin levels and number of patients involved, the value of the

statistically significant standard deviation (S.D.)* is also provided. Each bar in the graphs is labeled with two numbers; the upper one shows the number of patients represented and the lower one is the standard deviation.

The magnitude of the standard deviation is important in that it constitutes a measure of the scatter of the individual observations around their mean. As the magnitude of the standard deviation decreases, the certainty and reliability of the results increases; and it will be observed that the standard deviations throughout this study are low.

All data have been further analyzed statistically to demonstrate significance through determination of critical ratios (C.R.)† As the value of the C.R. increases, it becomes statistically allowable to attach greater significance to the conclusions drawn from the test.

Thus by this method it is possible to compare the means of any two tests to determine whether the difference is due to chance or is actually significant. In general, a C.R. value of two is considered very satisfactory since this means that the difference due to chance alone occurs only once in about 25 instances. Similarly, a C.R. value of three means that the difference due to chance alone occurs only once in about 370 instances.

With particular reference to this study, this means that important information of statistical significance can be extracted from the data through comparisons of critical ratios. Not only is it possible to compare the relative effectiveness of the different medications over the same time period, but it is also possible to measure

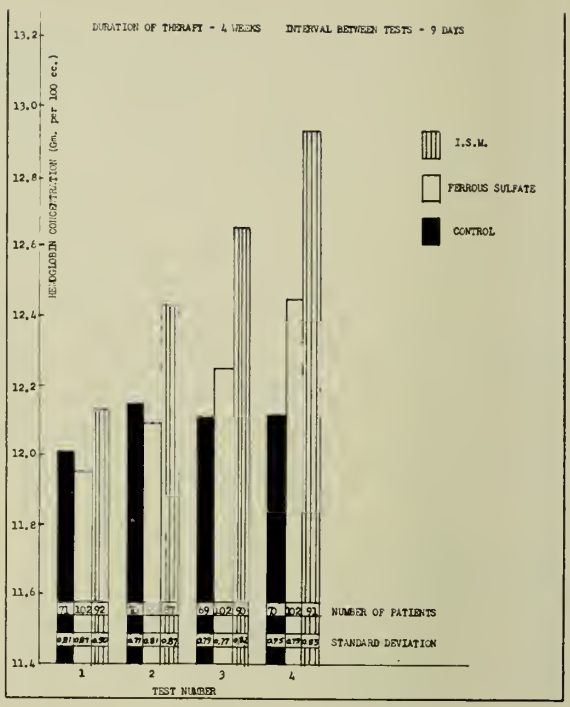


Fig. 1. All patients.

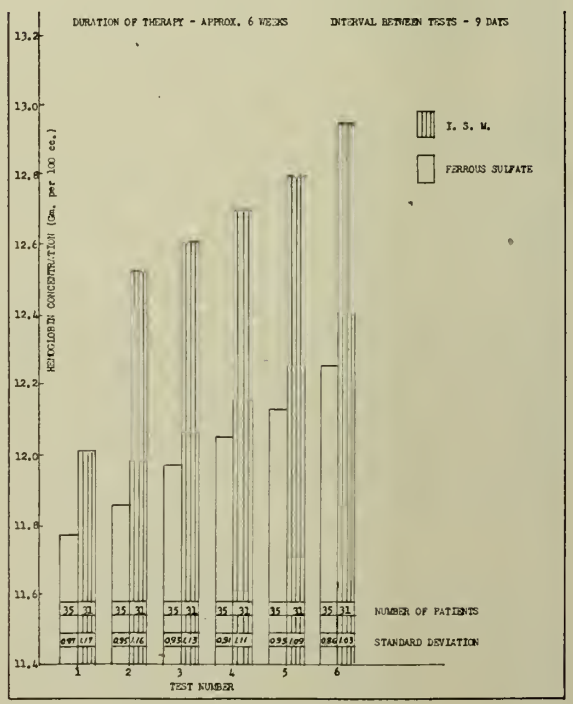


Fig. 2. Prenatal patients.

the rate of response for a given medication during any particular time interval between tests; and thus to draw accurate conclusions with regard to periods of accelerated and decelerated

*Standard deviations were calculated using the formula:

$$S.D. = \sqrt{\frac{\Sigma X^2}{n} - \left(\frac{\Sigma X}{n}\right)^2}$$

, wherein ΣX^2 is the sum of the squares of the individual observations, n is the total number of observations and $\left(\frac{\Sigma X}{n}\right)^2$ is the square of the mean of the observations.

†The value of the critical ratio between any two sets of observations is calculated from the formula:

$$C.R. = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{(S.D._1)^2}{n_1 - 1} + \frac{(S.D._2)^2}{n_2 - 1}}}$$

, wherein:

n_1 = number of observations, first set
n_2 = number of observations, second set
X_1 = mean of observations, first set
X_2 = mean of observations, second set
$S.D._1$ = standard deviation, first set
$S.D._2$ = standard deviation, second set

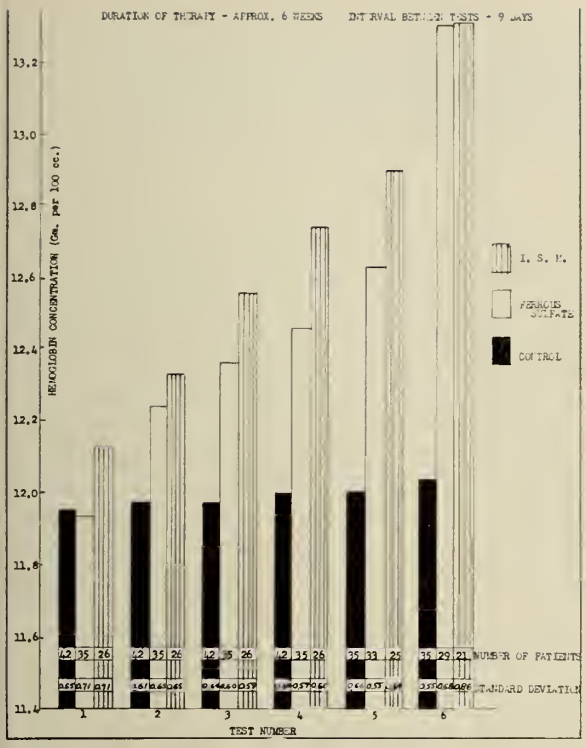


Fig. 3. Geriatric patients.

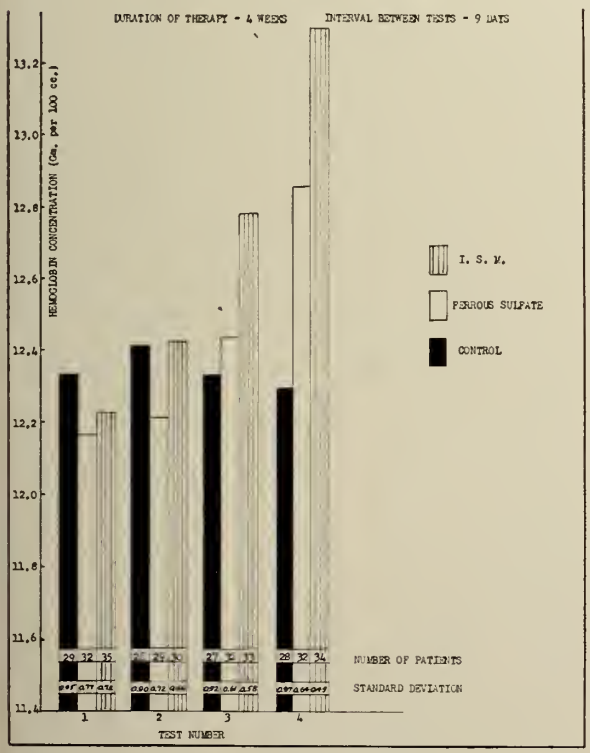


Fig. 4. Juvenile patients.

response. Comparison of data on basis of critical ratio values also tends to minimize the effect of slight differences in initial hemoglobin levels.

The most important critical ratios are the cumulative ones shown in tables V to VIII and portrayed in graphs V to VIII. Values shown are for the first medication period (involve the initial and second hemoglobin determinations), the first two medication periods (involve the initial and third hemoglobin determinations), and so on. Segmentary critical ratios covering each specific medication period (such as for example that which would cover the second medication period and would involve the second and third hemoglobin determinations) were also evaluated and analyzed for the possibility of yielding additional useful information especially with regard to periods of lag or accelerated response. However, analysis showed that these segmentary ratios yielded no information which was not deducible from the cumulative ratios. Graphs of the segmentary ratios are therefore not reproduced.

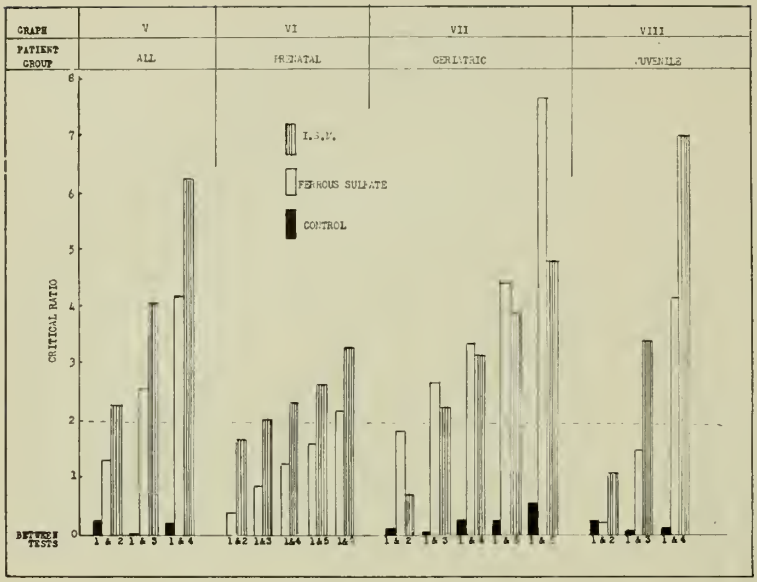
DISCUSSION OF DATA

A. *Combined data on all patients*

Graphs I and V represent the combined results for all patients. The absolute data with respect to hemoglobin increase is portrayed in I, while V deals with statistical significance as made possible through determinations of critical ratios. It is clear from V that the mean variation in the control group is small since the critical ratio never attains even a value of one. With the ferrous sulfate group, the critical ratio reaches the significant value of two during the second medication period, which means that the increase in hemoglobin in the ferrous sulfate group was not significant until that time. In the case of the I.S.M. group, however, V shows that the critical ratio of two is attained during the first medication period. Thus these patients attained a statistically significant increase in hemoglobin much sooner than was the case with the patients receiving ferrous sulfate.

B. *Data on prenatal patients*

The graphs for the prenatal group are II and VI. As in all cases the graph with the lower number provides the absolute data, and the one with the higher number relates to statistical significance. Absence of a control group in this study has already been noted. Graph VI shows that the patients receiving iron sodium malate experienced a significant increase in hemoglobin during the second period of medication since it was during this period that the critical ratio reached two. In the patients receiving ferrous sulfate, however, it was not until the fifth period



Figs. 5 to 8. Cumulative rations, all groups of patients.

of medication that this same significant increase was observed. In other words, the patients receiving the new product experienced a significant hemoglobin increase in less than one-half the time required in the case of ferrous sulfate. The gratifying early response to I.S.M. therapy in this group stands out prominently in graph II. Note the magnitude of the increase in the first medication period; i.e., the difference in heights of the first two I.S.M. bars as compared with the first two ferrous sulfate bars. It is also observed from II that in subsequent medication periods, the increments of increase under I.S.M. therapy are on the same order of magnitude as those obtained throughout with ferrous sulfate. However, note that the relatively large initial gain displayed by the I.S.M. group is maintained.

C. *Data on geriatric patients*

Results for the geriatric group are shown in graphs III and VII. Note that the critical ratio of the control group as shown in VII never attained a level of significance. With this group, the rate and magnitude of hemoglobin increase were approximately the same under both medications. In each series the critical ratio attained a significant level during the second medication period. In spite of the much greater response to ferrous sulfate during the last medication period, it will be observed that both groups of patients attained the same hemoglobin level at the conclusion of the test. It seems likely therefore that this represents the maximum hemoglobin level for this particular group of patients.

D. *Data on juvenile patients*

The findings in the juvenile group are illustrated in graphs IV and VIII. Here again, as portrayed in VIII, the control group behavior was statistically satisfactory, critical ratios always being well below one. Graph IV shows the more rapid response of the I.S.M. group and this is confirmed in VIII which shows that the minimum significant value of the critical ratio was reached in this group during the second medication period whereas it was not reached until the third medication period with the patients receiving ferrous sulfate. Graphs IV and VIII both show that this early advantage of I.S.M. over ferrous sulfate is not only sustained but actually increases throughout the entire test.

E. *Evaluation of side-effects*

These of course may be either favorable or unfavorable, and the bases on which they were judged in this study have been given hereinbefore. Reported results represent about 25 per cent of the total number of patients involved in the various tests. Of the number reporting, about 72 per cent recorded one or more unfavorable side-effects from ferrous sulfate medication whereas only about 8 per cent recorded similar undesirable reactions under I.S.M. therapy. Conversely, only 28 per cent of the reporting patients in the ferrous sulfate groups recorded favorable side-effects, whereas about 92 per cent recorded favorable side-effects under I.S.M. therapy. Enhanced well-being was especially evident in the juvenile and geriatric groups.

The general history of clinical evaluation permits the assumption that in all probability those patients who did not report on the study of side-effects did not experience unfavorable ones. And on this basis, approximately one out of every five patients receiving ferrous sulfate experienced distress of one sort or another. This is in sharp contrast with the results in the I.S.M. group in which only two patients out of a total of 92 reported unfavorable side-effects.

In the evaluation of such data, however, it must be remembered that there is a greater likelihood of reporting unfavorable rather than favorable data. In other words, the vast superi-

(Continued on page 79)

Section on PAIN

This section, which The Journal-Lancet *has set aside from time to time for articles and material on pain and distress, is rather of an experimental nature and can only succeed if it can be made interesting and worthwhile. Such a result can be attained if all who are interested would express their interest and make suggestions and offer material for the Section on Pain. The most marked difference between the February* 1953 *issue and the November* 1952 *issue is the omission of the Question and Answer portion. Opinions are solicited as to the value of questions and answers concerning pain.*

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Certain Small Painful Tumors of the Extremities

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The occurrence of localized pain with certain bulky neoplasms of the extremities is accepted as part of the clinical picture. Compression of large nerves by such new growths as lipomas, fibrosarcomas and desmoid tumors is observed commonly. Actual invasion of neural trunks is noted in large neurofibromas and angiomas, with resultant irritation of afferent sensory nerves and the production of pain that may occur locally or be referred over reflex pathways. Elevation of intraosseous pressure by marrow-displacing growths, such as Ewing's tumor, may cause pain early in the disease. Yet in all these instances, pain is to be regarded as an incidental and not a cardinal feature.

It is perhaps not so well known that certain small tumors of bone and soft tissue are associated with severe pain that is so characteristic as to be almost diagnostic of the underlying condition. In each instance the situation is amenable to surgical treatment. Yet without an awareness of the basic pathologic changes in these processes, such treatment often is delayed while protracted and unsuccessful attempts are made to effect relief by medical means.

I shall consider briefly 5 tumors of soft tissue and 1 tumor of bone in which pain is a high light in the symptomatology. None of these tumors produce gross tumefaction; few are even palpable and the osseous member is the only one that can be identified preoperatively. The lesions are not confined exclusively to the extremities but are commonest in these locations.

Malcolm Birt Dockerty *was graduated from Dalhousie University, Nova Scotia, in* 1934, *and received his M.D. from Minnesota in* 1937. *He is professor of pathology at the Mayo Foundation, University of Minnesota, serves as consultant and head of section A in the division of surgical pathology at the Mayo Clinic.*

PAINFUL NEUROFIBROMA

Case 1. A 54-year-old farmer registered at the Mayo Clinic on February 18, 1952. He complained of severe pain in the left heel that had begun as an intermittent pain on the inner side of his instep about two years previously. Extension down to the first and second toes and upward into the calf had been noted; the pain tended to occur in episodes lasting a few minutes to an hour. He had discovered early that an attack of pain could be initiated by manual pressure over the lower and inner aspect of the left calf "along the side of the heel cord."

Examination disclosed definite point tenderness in the trigger areas of the instep and, although no local tumefaction could be felt, it was deemed that operation was

*From the division of surgical pathology, Mayo Clinic, Rochester, Minnesota.

justified on the assumption that a local neural lesion was present.

At operation a spherical tumor 1.5 cm. in diameter was found encased within the sheath of the posterior tibial nerve. It was shelled out easily by blunt dissection, the neural trunk being left intact. The growth was a neurofibroma (figure 1).

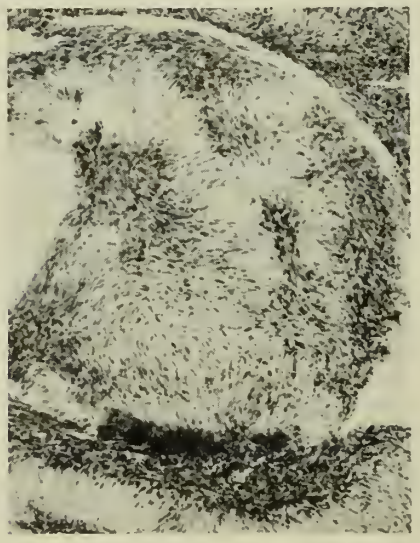

Fig. 1 (case 1). Neurofibroma featuring the nuclear palisading of narrow spindle cells. Fatty metamorphosis and the presence of bizarre, degenerating, giant cells are additional criteria for diagnosis (hematoxylin and eosin; x75).

Neurofibromas of peripheral nerves are single in 95 per cent of cases; in 5 per cent, the multicentricity characteristic of Recklinghausen's disease is exhibited. Paradoxically, as a group they are not particularly painful. In a study of a large series of such tumors, I have been unable to relate the type of distortion of the neural trunk to pain. The illustrative case is, therefore, reported to emphasize the importance of the inclusion of neurofibromas in this group of small painful tumors of the extremities.

The origin of these growths is ascribed variously to perineural fibroblasts and cells of the sheath of Schwann. Against the former theory is the observation that whereas the optic nerve has a fibrous investment it lacks endoneural compartmental division by means of Schwann cells and does not give rise to the tumor under discussion. Ninety-nine per cent of neurofibromas are benign.

AMPUTATION NEUROMA

Case 2. Twenty-two years prior to his first registration at the clinic on January 3, 1942, a 39-year-old salesman had undergone an amputation of the left leg at midthigh because of gas gangrene. He had been fitted with a prosthesis and had managed reasonably well for a period of ten years; he then noted onset of progressively severe muscular spasm and pain in the stump. Imbibition of alcohol and local injections of the latter in concentrated form had provided only temporary relief. Intensive treatment with roentgen rays likewise had been ineffectual.

Examination disclosed extensive actinodermatitis over the stump. No mass was evident but the entire region was tender to deep palpation. Roentgenograms disclosed multiple bony spurs projecting from the stump of the femur. Reamputation was advised but was declined by the patient.

By the time of his second admission to the clinic, in 1950, the patient had become addicted to alcohol and was verging on addiction to opiates from his effort to meet the problem of pain and muscular spasm in the affected part. Severe and explosive pain occurred in episodes at any time of the day or night. Attacks were marked by sudden onset of sharp, shooting pain that often extended into the left hip. Duration was from a few minutes to several hours. Soreness between attacks was such that for a year he had been able to wear his prosthesis only for short periods.

Revision of the amputation stump was done on August 10, 1950; a traumatic neuroma 5 by 3 by 2.5 cm. was found that formed an onion-like expansion on the distal end of the left sciatic nerve (figure 2*a* and *b*).

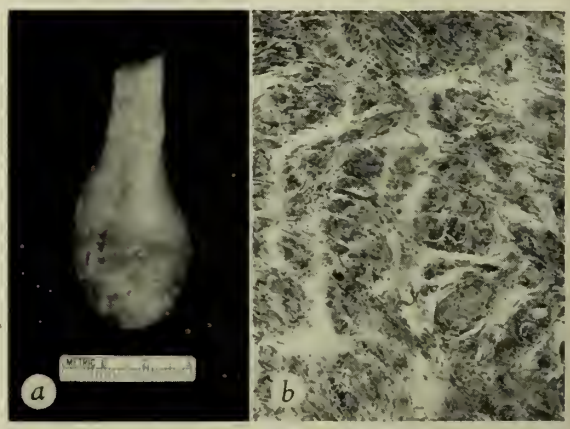

Fig. 2 (case 2). *a.* Amputation neuroma showing the onion-bulb arrangement which usually caps these small painful growths. *b.* Axis cylinders surrounded by mantling cells of neurilemma make up the clusters of individual cells, which propagate aimlessly among the bundles of fibrous tissue (hematoxylin and eosin; x60).

The designation "traumatic neuroma" is preferred to "amputation neuroma" since complete severance of a nerve is not required to produce a lesion like the one illustrated. Traumatic interruption of some neural fibers is, however, implicit in the definition. The pathogenesis of neuromas after such interruption is briefly as follows:

After the well-known process of wallerian degeneration has effected lysis as far proximally

as the first node of Ranvier, the nerve begins to regenerate. Numerous axis cylinders with bulbous tips sprout from the cut end of the nerve; around these the cells of the neurilemma (Schwann cells) proliferate and provide a protecting mantle. An insulating cover of myelin is produced more slowly. Invasion of the scar tissue of the stump in a search for the distal end of the severed nerve results in an aimless wandering of the newly invested axis cylinders. The bulbous whorl of neural and fibrous tissue depicted in figure 2*a* and *b* is often the painful end product.

SCLEROSING NEUROMA

Case 3. A 55-year-old clerk registered at the clinic on August 15, 1945, because of pain in the fourth right toe. This pain had been present intermittently for nine years and had begun one year after the patient sustained minor injury to the right foot. Occurring in explosive attacks, the pain took the form of lancinating spasms that involved the plantar aspect of the affected toe and extended proximally as far as the knee. Sometimes the attacks were precipitated when the patient walked but they also occurred when he was in bed. Duration was variable; the onset and termination were abrupt and the severity of pain frequently induced nausea.

On examination it was remarked that the patient wore shoes which appeared too small for his feet. Pronounced tenderness was noted to deep manual pressure over the plantar aspects of the heads of the third and fourth metatarsals. No tumor could be palpated.

At operation on August 22, 1945, a large (1.5 cm.) sclerosing neuroma was removed from the main trunk of the fourth digital nerve. The proximal and distal portions of the nerve appeared to be normal (figure 3*a* and *b*).

Sclerosing neuroma (Morton's toe) is for the most part an affliction of women. This is owing to the high-heeled design of the "prison cells of pride" that conceal their feet but at the same time compress the digital nerves which course near the plantar surface. An observed predilection for the fourth nerve on the part of the lesion in question relates to the dual composition of this nerve plus the fact that its component radicles loop over the plantar surface of the short digital flexor muscles (figure 3*c*). The cramping effect of tight shoes accentuates the stretching of this exposed neural loop during dorsiflexion of the foot, as in walking, and trauma results. Edema, demyelinization and fibrosis combine with proliferation of cells of the neurilemma to increase the bulk of the affected segment and further predispose the nerve to trauma. The paroxysmal pain and focal tenderness originally induced by trauma and somewhat relieved by use of wide shoes and transverse metatarsal bars is perpetuated by irritation and irreversible fibrosis. However, the latter rarely effects complete replacement of the neural trunk, and thus pain persists until the causative neuroma is excised. To accomplish this a dorsal or web-splitting incision is advised.

Interesting side lights to this condition include the involvement of digital nerves other than the

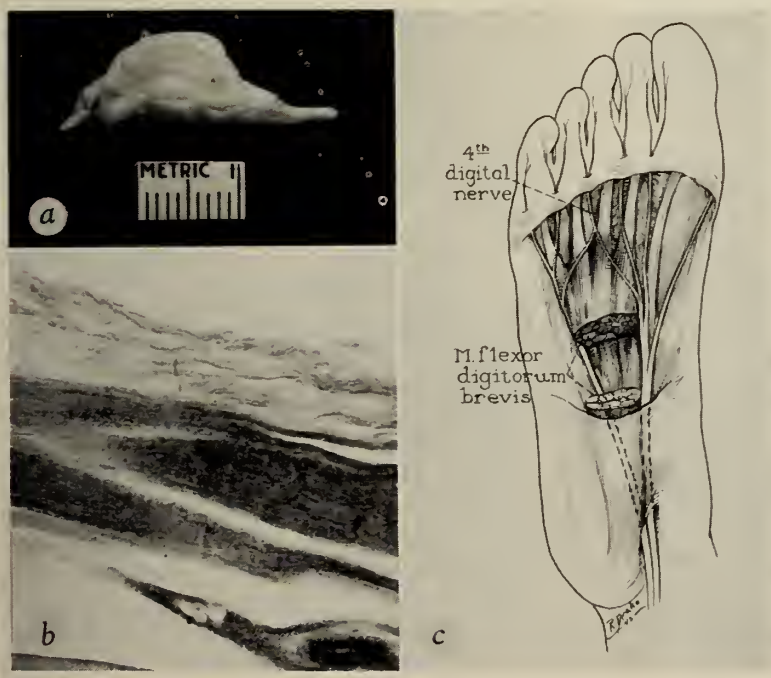

Fig. 3 (case 3). *a.* Sclerosing neuroma of average dimensions, forming a distinct bulge on the resected fourth digital nerve. *b.* Neural and perineural fibrosis and edema combine with reactive proliferation of cells of the neural sheath to typify the lesion (hematoxylin and eosin; x60). *c.* Dual derivation of the fourth digital nerve and the superficial position of its constituent roots.

fourth, the occurrence of multiple and even bilateral neuromas and the occasional appearance of an amputation neuroma at the operative scar.

GLOMUS TUMOR (GLOMANGIOMA)

Case 4. A 26-year-old housewife registered at the clinic on May 17, 1948. She had experienced pain and weakness in the left leg for thirteen years. Her trouble had begun with discovery of a region of hypersensitivity behind the left knee, together with the occurrence of sharp, shooting pains in this location. Both pain and tenderness apparently were aggravated by exercise and both had become progressively so severe as to interfere with performance of her daily duties about the house. Active and passive movements of the knee had become so painful that for the past year she had been able to walk only with the left knee fixed in either extension or flexion. Both weakness and atrophy of the left leg had progressed.

Diathermy had been of no avail and chiropractic adjustments were intolerable because of pain and tenderness.

General and neurologic examinations disclosed no constitutional cause for the local condition. The left calf was 2 inches (5 cm.) less in circumference than the right. An area 2 by 2 cm. in the left popliteal space at about the level of the knee was so exquisitely tender that the diagnosis of glomangioma was suggested by several consultants. No local tumefaction could be palpated.

At operation on May 28, 1948, local infiltrative anesthesia was induced to allow exploration of the circumscribed zone of tenderness. Exposure and retraction of the common peroneal nerve elicited the usual amount of discomfort. Beneath the nerve, however, dissection of the loose areolar tissue triggered such an explosive spasm of pain that general anesthesia was required before the surgeon could proceed. An encapsulated, reddish-blue tumor 2 cm. in diameter was encountered just above the level of the knee, near the periosteum of the lower end of the femur. This tumor was unattached to any identifiable nerve or other structure and was shelled out without difficulty. Microscopically, it proved to be a glomangioma (figure 4).

In simplest terms, a glomus tumor is a macroscopic expansion of a normal arteriovenous anastomosis known as a "glomus." As depicted in figure 5, the latter structure consists of an afferent arteriole, a departing venule, one or more thick-walled connecting channels that are not capillaries and an overabundant complement of neural fibrils. Designed by nature as an automatic thermostat that operates by shunting blood directly from arteries into veins, the nucleus of the mechanism lies in the cells that invest the connecting channels or canals. These cells, now commonly referred to as "pericytes," combine the properties of endothelial and contractile smooth muscle cells. Under the influence of local neural reflexes, they respond in the desired manner by contracting or relaxing with consequent closing or opening of the canals.

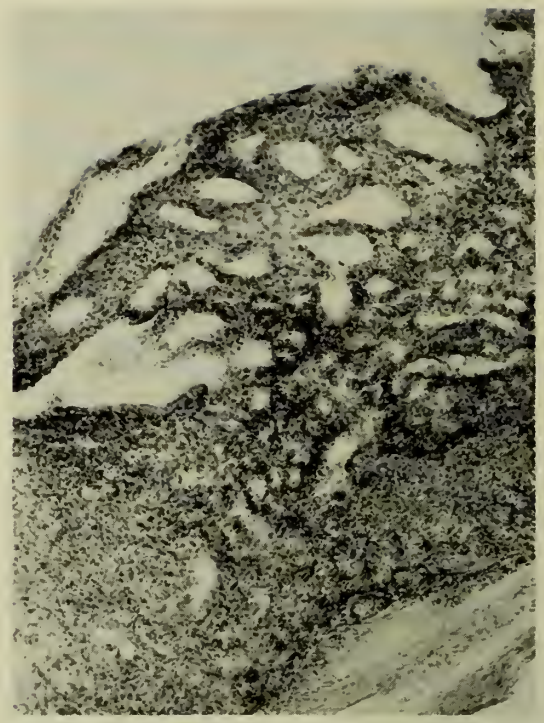

Fig. 4 (case 4). Glomangioma; the arteriovenous canals are surrounded by sheets of pericytes that, in the lower portion, appear to occupy the entire region (hematoxylin and eosin; x 80).

Glomus tumors feature proliferation of all the normal constituent units of the glomus. The pericytes and the canals are most prominent, however, and special stains are necessary to demonstrate neural filaments. The tumors are encapsulated and benign. Examples that exceed 1 cm.

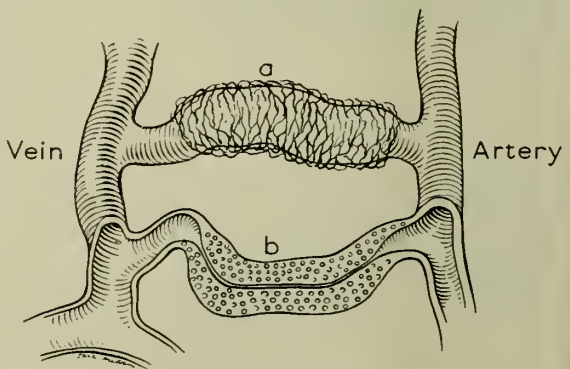

Fig. 5. The arteriovenous short circuits seen in a normal glomus. The diagram shows the webbing of nerve filaments (a) and the clusters of pericytes (b).

in diameter are the exception rather than the rule. Because of their predilection for the extremities, especially the upper extremity, one third of the 100 or more such tumors reported in the literature are subungual in location. Involvement of deeper structures, as in the case presented, is distinctly uncommon.

PAINFUL VASCULAR MYOMA

Case 5. A 45-year-old housewife registered at the clinic on April 2, 1952, for a general examination. Among her several complaints she stated that a small tumor on the left ankle had bothered her for twenty years. Exposure to cold and local trauma, even in the form of mild pressure, was prone to produce sharp pain in the region. This pain would last for periods as long as fifteen minutes. No increase had been noted in the size of the growth over the period of observation.

Examination disclosed a pea-sized, movable, subcutaneous tumor on the outer aspect of the left ankle. No discoloration or other abnormality was noted in the overlying skin. Manipulation of the tumor produced rather severe pain that did not extend in any direction.

The tumor was removed without difficulty through a simple incision. Grossly, it was well encapsulated, brownish gray and firm. The resemblance to a small uterine fibroid was so striking that the diagnosis could be made macroscopically (figure 6*a*).

Microscopically (figure 6*b*), the composition was that of elongated smooth muscle cells that were for the most part arranged concentrically about blood-vascular spaces of small caliber. The ratio of the wall to the lumen in these structures was such that without knowledge of the clinical history or cognizance of the existence of this type of tumor a diagnosis of simple fibromyoma would have been rendered. A few neural twigs could be demonstrated by means of special stains employing silver but the typical neural fibers of neurofibroma were absent.

Vascular myoma, like its close relative the glomus tumor, is prone to be small, painful, subcutaneous and confined for the most part to the extremities. The digits, however, harbor the lesion but rarely. Its origin can be traced in about half the cases to local blood vessels of the involved region. Actual contraction of the constituent muscle with knotting of the tumor has been observed at operation; this phenomenon apparently is related to triggering of the painful spasms observed clinically. Injection of epinephrine into the tumor substance has produced a like effect.

According to Murray and Stout,[1] the source of the muscle in these tumors is identical with that of the pericytes previously described for the glomus tumor. By means of tissue cultures, these authors apparently were able to trace transitions from adventitia-like cells through pericytes to a final stage in which the elements contained myofibrils. Histologic confirmation of this concept was afforded by apparent transformation of pericytes into smooth muscle cells in the peripheral portions of certain glomus tumors.

OSTEOID OSTEOMA

Case 6. A 24-year-old farm helper entered the clinic on April 3, 1952, because of severe pain in the left leg.

Eleven months prior to registration and after possible trauma from resting heavy bags of commercial fertilizer on his left thigh he began to experience deep "bone pain" in the region. Most of this pain localized to the midanterior aspect of the thigh, but at times it was situated posteriorly and occasionally affected the left knee. Exercise and exposure to cold made the pain worse; acetylsalicylic acid in large doses controlled it.

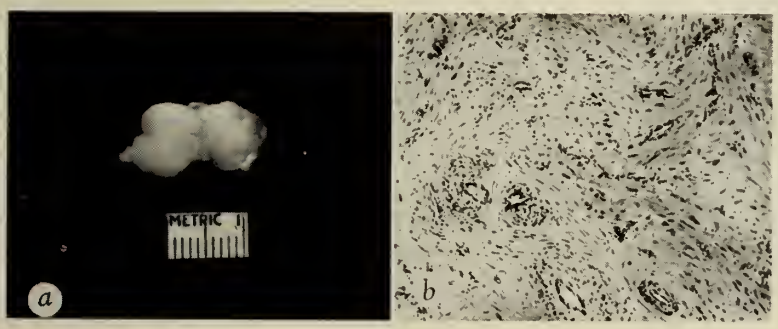

Fig. 6. Vascular myoma. *a.* (From a case similar to case 5). Note the small size and encapsulated appearance of the lesion. *b.* (Case 5). Numerous blood-vascular spaces coursing through a myomatous matrix (hematoxylin and eosin; x70).

Atrophy of the leg was noted three months after the onset of the pain. Four months prior to registration constant pain in the lower part of the back developed; this pain extended into the left buttock. Roentgenograms of the spinal column taken elsewhere presented suggestive evidence of a protruded intervertebral disk but myelographic studies were not done.

On examination the patient walked with a limp on the left side and a slightly stiffened back. The circumference of the left thigh was 2 cm. less than that of the right. Although the symptoms were consistent with a protruded intervertebral disk, the test of raising the straight leg was negative and the knee and ankle reflexes showed no deviation from normal. Attention directed to the left thigh disclosed a sharply circumscribed region of deep tenderness on the anterolateral aspect 15 cm. above the knee.

Roentgenograms of the thoracic and lumbar portions of the spinal column appeared normal but a roentgenogram of the left thigh disclosed a wide zone of cortical osteosclerosis containing a tiny radiolucent center. This was typical of the appearance of osteoid osteoma. The wedge of cortical bone removed at operation on April 10,

1952, encompassed a tiny, soft, central, osteoid nidus, commonly referred to as an osteoid osteoma (figure 7).

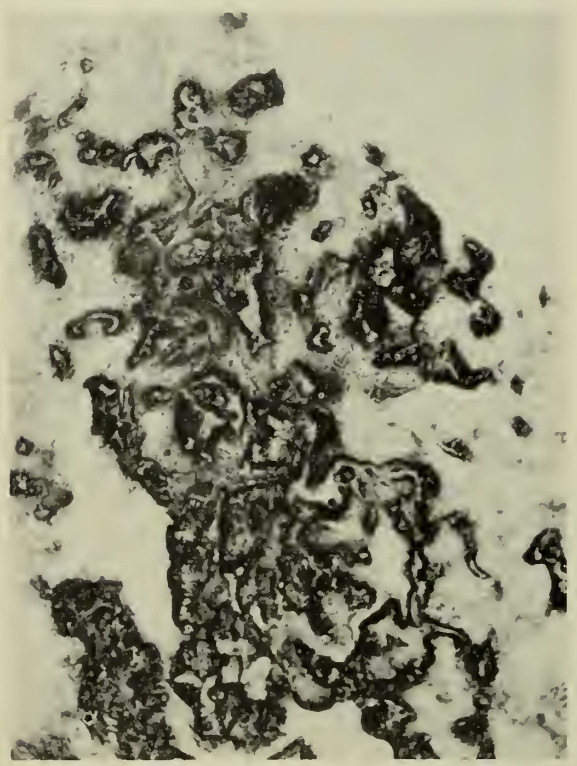

Fig. 7 (case 6). Nidus of osteoid osteoma featuring a fine mosaic of calcifying osteoid tissue in a fibrovascular matrix. This photomicrograph encompasses the entire nidus and emphasizes the diminutive size of these tumors (hematoxylin and eosin; x60).

The literature now contains many reports of this midget type of tumor, which was originally described by Jaffe[2] as an oncologic entity that heretofore had been confused with and often mistakenly diagnosed and treated as sclerosing osteitis. Almost every bone of the body has been reported to harbor this neoplasm, but the bones of the extremities are most frequently affected. Most of the patients are young males. Typically, the pain is not severe but is unrelenting and often interferes with sleep.

Pathologically, the important component of the lesion is the central nidus, which consists of a vascular bony mesenchyme rich in osteoblasts and osteoclasts. Within this matrix, immature bony trabeculae are deposited; these may later calcify and change the roentgenographic appearance from that of relative lucency to that of opacity. No marrow is found within the nidus. The ridiculously small size of the nidus contrasts with the extensive zone of osteosclerosis. The pathologic basis for this sclerosis and for the pain that attends the presence of the nidus is obscure. Complete surgical removal of the nidus is better treatment than the various bone-shaving procedures formerly employed. The condition is benign.

The illustrative case is presented as only 1 out of possibly 30 or 40 instances of this condition that my colleagues and I have encountered; it is the seventh case in which the symptoms and signs were confusingly similar to those of protruded intervertebral disk.

SUMMARY

The causes, character and pathways of extension of pain are legion; the underlying factors are often more clearly displayed by the soul searching of the psychoanalyst than through manipulations of the microscopist.

Six interesting groups of insignificantly small tumors are described in which local pain is usually an outstanding and frequently a diagnostic symptom. These tumors are amenable to surgical treatment.

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Low Back Pain—Referred Pain from Deep Somatic Structure of the Back

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PAINFUL DISABILITIES of the back and the extremities are frequently caused by muscle action which produces a tear of the lumbo-dorsal fascia at one, or both, of two sites in the lower part of the back. The result of this injury is pain, aroused in the damaged tissues and referred to other portions of the body, in accordance with a spinal segmental pattern of distribution. The end product of the anatomic derangement, combined with the accompanying pathophysiologic effects, represents the most common clinical form of back pain.

Investigations by Copeman and Ackerman[1] disclosed the occurrence of fat herniations through the deep fascia and also supplied valuable information on the "basic fat pattern." The herniations were considered as "a comparatively advanced stage of the disease process," with edema of the fat lobules as an antecedent disorder and responsible for "minor and less localized degrees of pain."

Although similar observations were made,[2] it became apparent that these conditions were inadequate for the solution of problems more frequently encountered and more complex in nature. The pathologic picture of herniation and edema of fat lobules presented possibilities for correction of certain symptom-complexes but failed to explain satisfactorily many other features of disability. Continued search for abnormalities of the lumbo-dorsal fascia and related structures led to discovery of more impressive pathologic changes.[3]

ANATOMIC ABNORMALITIES

Information on structural changes was obtained from findings at operation in 19 consecutive cases, including 14 previously reported. All the surgical procedures were carried out at one, or both, of two sites in the lower part of the back—the midsacral paraspinal region and the midlumbar region over the lateral portion of the sacrospinalis muscle. Predisposition to injury of the fascia at these locations is probably determined by contraction of muscles attached to the fascia at these points—the latissimus dorsi in the midlumbar region and the gluteus maximus in the midsacral region.

In the 19 patients subjected to operation, 29 sites were explored. In four, the objective was a correction of the latissimus dorsi syndrome; the operation consisted of division of portions of the latissimus dorsi muscle in the midlumbar region. In this procedure no anatomic abnormalities are encountered; the evidence for participation of this muscle is obtained by physiologic methods. In two of the four patients, the subfascial space was explored and no fat tissue was found.

The typical pathologic lesion, found in 20 of the remaining 25 sites, consisted of fibrosis of the subfascial fat with adhesions to the ventral surface of the fascia. At two sites the subfascial fat was normal grossly but showed inflammatory changes on microscopic examination. At two sites the fascia was distended and very thin and the subfascial fat contained numerous enlarged, edematous lobules. At one site the tissues were normal.

The initial injury is probably a rupture of the fascia, caused by contraction of portions of muscles attached to it at the site of the tear. In the process of healing, restoration of continuity of the fascia is usually complete except for small defects in some cases. Whether the original injury caused any damage to the subfascial fat has not been determined. The relationship of the layer of subfascial fat to the overlying fascia provides the opportunity for development of adhesions between the two structures.

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In the fully developed lesion, as seen at operation, the fascia is frequently thinner than normal. After incising the fascia, the subfascial structures are usually found to be adherent to the ventral surface of the fascia. The fibrous strands are delicate and dissection can be carried out without difficulty. The degree of fibrosis of the subfascial tissues varies considerably. The extent of the fibrous attachment of the tissues to the fascia cannot always be accurately determined; as a rule, the area of dissection extends about one inch transversely and two inches vertically.

Microscopic examination of the tissues removed from the subfascial space reveals varying degrees of fibrosis of the fat lobules; in some specimens inflammatory changes are found. In several specimens consisting of the fascia together with the subfascial tissues, fibrous connections were found between the two structures.

The pain arising in abnormal tissue of this type is probably caused by traction on the subfascial tissues which are well supplied with blood vessels and nerves. The influence of traction and manipulation of these structures in provoking pain has been repeatedly observed at operation. Tissues deranged in this manner are considered as the most common primary source of painful impulses (trigger-point or algogenic area) in cases of disability of the back.

PATHOPHYSIOLOGIC EFFECTS

Discussion is limited to telalgic phenomena and autonomic nerve reactions. The former, referred pain and referred tenderness, are sensations which arise at the primary source of impulses and are transmitted to other parts of the body.

Review of literature. Knowledge of referred phenomena from mesodermal structures is a relatively recent development. Following a suggestion by Lewis,[4] experiments were undertaken by Kellgren.[5] These consisted of injections of hypertonic salt solution into muscles and other tissues of the back, using human volunteers as subjects. Lewis and Kellgren[6] continued the experiments by injecting the interspinous ligaments at various levels and charting the locations in which referred pain and referred tenderness became evident. Attention was called to the spinal segmental distribution of referred phenomena. Campbell and Parsons[7] injected hypertonic salt solution into various deep structures about the head and neck and thereby produced referred pain and referred tenderness to the head; the manifestations were similar to those noted in the "posttraumatic head syndrome." From these observations they considered it possible to have pain transmitted to the head from lesions in the lower portions of the back, even from the dorsal and the lumbosacral levels. Inman and Saunders[8] used various methods of irritation of the deep structures of the extremities and studied the location and direction of referred pain. This was mapped out in two planes,—the superficial musculature and related structures, and the deeper lying tissues as bone, periosteum, ligaments and tendons. Weddell, Sinclair, Feindel and Falconer[9] repeated the experiments of Lewis and Kellgren by injecting hypertonic salt solution into the interspinous ligaments, using roentgenographic control for more accurate localization. They contended from their observations that referred pain could be produced only if a nerve trunk is irritated. Sinclair, Weddell and Feindel,[10] in an extensive critical analysis, reviewed the entire subject of referred pain. They concluded that the anatomical basis of referred phenomena is the branched axone; they rejected the opinion held by others that reference is provided by connections in the central nervous system. Regarding the distinction between referred pain and referred tenderness, they state "in any given case there are two main mechanisms at work; the first of these is the misinterpretation by the central receiving apparatus of the source of the impulses, and the second is the production in the periphery, as a result of antidromic impulses, of metabolites which at first stimulate the nerve endings there and later damage them. It is probable that the operation of the first of these mechanisms gives rise chiefly to referred *pain*, while the chief result of the operation of the second is referred *tenderness*, but both mechanisms must be considered in relation to either phenomenon."

Characteristics of referred phenomena. The occurrence of sclerotomic reference of pain and tenderness is apparently accepted by most investigators. This implies that the telalgic effects may appear in any other deep somatic structure which receives its afferent supply from the same spinal nerve as that in which the noxious impulses originate. According to Inman and Saunders, ". . . the precise distribution of the pain appears to be definitely segmental in character in so far as the skeletal structures are concerned and this segmental distribution in nó way corresponds to that of the skin."

Contralateral reference occurs in most patients handicapped by chronic backache. The distribution of both the pain and the tenderness corresponds to that of the injured side, though usually it is less extensive. It is not unusual to find the principal features of painful disability to be traceable to lesions in the opposite side of the body.

The controversy regarding reference by peripheral or central channels is unsettled. For practical clinical purposes this is of minor importance, although a more adequate solution would be desirable.

Reference in continuity of a nerve trunk distal to the level of irritation is apparently a subject of interest. Contrary to a widely held belief, telalgia is not limited to the direction and extent implied by that term.

The contention by Weddell, Sinclair, Feindel and Falconer[9] that reference requires irritation of a nerve trunk is unfounded. The clearest illustration of this, in clinical cases, is the ease with which reference can be demonstrated from the terminal fibers in the latissimus dorsi muscle in which no large nerves are found.

It may be pointed out that the experimental use of muscles to determine the direction and extent of sclerotomic pain may lead to confusing results for the reason that most muscles are innervated by more than one spinal nerve.

A secondary, or reference area of tenderness frequently exhibits the same characteristics as the primary site of pain. This applies chiefly to radiation of pain on irritation; further, with anesthetization of a reference area, the pain and tenderness may be eliminated temporarily or permanently. The response of the reference area to these procedures may, therefore, easily lead to errors in the interpretation of the real source of the pain. The relief of pain from such an area by use of local anesthetic or other measures can hardly be criticised, but it may be assumed, as a therapeutic axiom, that treatment should be directed toward the primary lesion if that is recognized and accessible for correction.

Autonomic nerve reactions. These have been mentioned by several investigators of the nature of somatic pain. Campbell and Parsons found in their experimental subjects the frequent occurrence of autonomic (pallor, nausea, sweating, alterations of pulse) and equilibritory (listing, giddiness) concomitants. Inman and Saunders mention sweating, blanching and nausea as accompaniments of pain and resulting in some instances in complete collapse of the experimental subject. According to Wolff and Wolf,[11] "The management of pain constitutes a serious clinical problem, not only because of itself, as a distressing experience, but also because continued pain has been demonstrated to have deleterious action upon such vital organs as the heart and kidneys." Kuntz[12] states "Afferent impulses arising in any part of the body may elicit reflex reactions carried out by autonomic nerves."

One manifestation which is evidently due to autonomic nerve activity is dizziness. This is not uncommon among patients with painful disability. The mechanism is apparently set up by painful impulses arising in the latissimus dorsi muscle. Relief was obtained in two patients so afflicted, among fourteen subjected to operation.[3] In one of these the condition recurred and it was found repeatedly that attacks could be eliminated by anesthetization of the tendinous portions of the origin of this muscle in the midlumbar region. More lasting relief was obtained by surgical resection of the tendinous fibers of the aponeurosis proximal to the level of origin of the painful impulses.

A clinical feature seen commonly is anesthesia or hypoesthesia of the extremities. This appears in the form of an annular or "glove and stocking" distribution. Conventionally, this type of disturbance is assumed to be pathognomonic of hysteria. It has been found to be reversible, in whole or in part, following correction of the anatomical abnormality which is responsible for the pain. Sensation can be restored temporarily by anesthetization of the algogenic site.

It is necessary to consider the possibility of autonomic nerve activity as a factor in referred tenderness. This phenomenon has been regarded as a result of liberation of metabolites at the site of the hyperalgesia. Being a chemical process, it could most conveniently be explained as a reaction of the autonomic nervous system. On the other hand, it is also clearly restricted to the extent of the sclerotome, suggesting a form of behavior which is not characteristic of autonomic nerve activity. The identity of the chemical so deposited is unknown. Lange[1] suggested that it is lactic acid, liberated as a result of autonomic nerve dysfunction. It appears that the viewpoint held by others, regarding the chemical factor in referred hyperalgesia, receives support from the observation that a period of 3 to 4 hours is required for elimination of the

tenderness following anesthetization of the trigger-point.

Diagnostic methods. The only procedure which is considered necessary, apart from clinical examination, is local anesthetization of the algogenic area. With recognition of two sites of predilection for injuries of the lumbo-dorsal fascia, the problem has been simplified. The injection is made subfascially at the location of the trigger-points in the midlumbar and the midsacral regions. For anesthetization of the latissimus dorsi muscle, the injection is carried out in the tissues superficial to the fascia and slightly proximal to the site of tenderness.

A successful injection is expected to provide complete or substantial relief which is usually temporary. Among the causes of failure are incomplete anesthesia; injection of one trigger-point and overlooking another; and injection of a reference area instead of the trigger-point.

The total content of discomfort in the patient consists of pain arising at the trigger-point, referred pain and referred tenderness. With a successful anesthetization of the trigger-point, all pain and tenderness at that site will disappear promptly within a few minutes; this applies also to the component of referred pain. Referred tenderness, however, requires a period of three to five hours for subsidence; during this period of time the anesthetic effects have usually worn off and referred pain again becomes evident. Due to this overlap in time relations between referred pain and referred tenderness, the patient may never become completely free from discomfort, in spite of a successful anesthetization of the trigger-point. It has, for that reason, become a practice to repeat the anesthetization about two hours after the initial injection, in order to prolong the anesthetic effects. This provides a longer period of relief for evaluation of the response to the injection.

CLINICAL OBSERVATIONS

Correlation of the anatomic and the pathophysiologic aspects led to the definition of three distinct clinical pictures, explainable as sclerotomic manifestations derived from the impulses at the sites of injury. From study of the pain charts of Inman and Saunders, it was possible to identify one clinical picture which is interpreted as a second lumbar nerve syndrome. With this, the patient locates the pain, almost invariably, in the lower lumbar, the upper sacral and the sacroiliac regions. Usually tenderness is a prominent finding in these locations. The complaints less often are centered on the groin or along the iliac crest. This syndrome results from pain arising in the subfascial tissues in the midlumbar region. Verification of this relationship has been satisfactorily established by observation of relief, obtained temporarily by local anesthetization and permanently by surgical correction of the anatomic derangement.

A similar relationship exists between the structural abnormalities in the midsacral region and referred phenomena within the sclerotomic limits of the first sacral nerve. The subjective and objective features are located most conspicuously in the lower portion of the buttock, with or without radiation of the pain distally in the posterior part of the thigh and in the lateral aspect of the thigh, leg and foot. In some cases, the clinical picture of coccygodynia results from the impulses aroused in the midsacral region.[14]

A third syndrome has been predicated on the basis of involvement of the latissimus dorsi muscle. A portion of this muscle has its anatomic origin from the lumbo-dorsal fascia through an aponeurosis which evidently extends over the fascia as far distally as the sacral level. With injuries of the fascia, the tendinous slips of this aponeurosis, including their afferent nerve supply, would likewise be damaged. Under those circumstances, the radiation of pain is toward the upper portions of the body within the afferent distribution of the sixth, seventh and eighth cervical nerves. The clinical pictures are often diagnosed erroneously as neuritis, fibrositis, arthritis, myositis or bursitis. This pathway of reference is frequently associated with headache by radiation to the paraspinal muscles supplied by the sixth, seventh and eighth cervical nerves.[15,3] The most common clinical forms of disorder are those involving the shoulder and the scapular region.

More accurately, it may be pointed out that the sixth, seventh and eighth cervical nerves provide innervation for practically all the deep structures of the shoulder and the upper extremity, the infraspinatus, the scaleni, the pectoralis major and minor, the serratus anterior, the spinal and paraspinal structures of the cervico-dorsal region and the latissimus dorsi. In accordance with principles of reference, clinical manifestations may appear in any of these portions of the body, transmitted from a trigger-point in the aponeurosis of the latissimus dorsi muscle.

Any of the three separate syndromes may ap-

pear in isolated form. More frequently combinations of two, or all three, are found in the same patient.

TREATMENT

With a structural derangement of the tissues as has been demonstrated, it is obvious that only surgical correction can be expected to provide relief. This consists of exposing the fascia at the trigger-point, incising the fascia and removing the fibrosed tissues. The technique is similar for the sacral and the lumbar regions. Drainage of the operative field is maintained for a period of five to seven days to prevent accumulation of sero-sanguinous fluid and recurrence of symptoms.

In case of isolated latissimus dorsi syndrome, treatment consists of resection of the tendinous fibers of the aponeurosis above the level of tenderness. The pathologic picture in this disorder is not clear although it is reasonably certain that irritation of the terminal portions of the tendon of origin is responsible for the clinical manifestations. When the latissimus dorsi syndrome is associated with either, or both, of the other syndromes, it ordinarily requires no special attention.

Results of treatment. In four cases, resection of portions of the aponeurosis of the latissimus dorsi was carried out, all in the midlumbar region. In two of these, disability of four to six weeks duration involving the scapular region was the cause of complaint; in one the manifestations were chiefly in the lumbar region. Following operation, relief was complete and no recurrence of symptoms developed during periods of 11 to 13 months of observation. In two of this group, no fat tissue was found in the subfascial space. In the other case, painful rigidity of the neck was partly relieved.

In five cases, the midsacral region alone was the site of the painful lesion. In four, relief was complete; in one a painful adherent scar developed. All were able to resume their regular work. No recurrence was found during periods of observation varying from four to 20 months. In one patient, symptoms and objective findings of midlumbar syndrome have developed and may require additional treatment. In two cases, the latissimus dorsi syndrome was combined with the sacral lesion; this was eliminated in one and improved in the other.

The midlumbar region was explored in two cases. In one, the tissues were normal and no significant relief was obtained; it was subsequently determined that the pain arose from the sacral region for which she refused further treatment. In the second case, pain in the lower part of the back, associated with painful disability of the shoulder, was corrected; no recurrence was noted in either the back or shoulder during the observation period of 16 months.

In eight cases, both the midsacral and midlumbar sites were injured; in one of these the abnormality was bilateral. In six cases, the latissimus dorsi syndrome was included. The combination of midsacral and midlumbar syndromes was found, in all cases, on the same side of the body. The operative procedure was carried out at both levels, with one exception, at the same time. In one patient who insisted on having a general anesthetic for the operation, part of the lesion in the lumbar region was missed and only partial relief was obtained; the subfascial tissues appeared normal grossly but showed evidence of inflammatory changes on microscopic examination. In all others of this group, distinct abnormalities of the fascia and subfascial tissues were found. This group included two patients who were subject to attacks of dizziness. Also included in this group were four patients in whom the annular or "glove and stocking" type of sensory disorder was found; following operative correction, sensation was restored so that it was normal subjectively and only slightly subnormal objectively. In three cases the hand was involved and in one the lower extremity below the knee. In six cases of this group, relief from pain and associated disability was complete; in the remaining two, partial relief was obtained and additional surgical correction is necessary.

SUMMARY

The anatomic arrangement of the human body provides a predisposition to injury of the lumbo-dorsal fascia at two principal sites in the lower part of the back. The damage consists of rupture of the fascia by muscle action. With healing of the defect, fibrosis develops between this structure and the subfascial fat.

From a painful lesion thus developed, the impulses are referred to other skeletal structures in accordance with a spinal segmental (sclerotomic) pattern of distribution. Referred phenomena include pain and tenderness,—exhibiting similarities and differences which must be recognized for an adequate interpretation of clinical features. The reactivity of the autonomic nervous system to painful stimuli may aggravate or confuse clinical pictures, thus adding to the complexity of the disorder developed by somatic nerve effects.

The combination of somatic and autonomic nerve reactions represents the symptomatology for which the patient seeks relief. Three syndromes have been recognized,—a midsacral, or first sacral nerve, syndrome; a midlumbar, or second lumbar nerve, syndrome; and a

latissimus dorsi syndrome, in which the clinical features appear in the sclerotomes of the sixth, seventh and eighth cervical nerves. These may appear singly or in combination.

Treatment consists of surgical correction of the anatomic abnormality. The results of 29 operations in 19 patients have been satisfactory in providing prompt, adequate and lasting relief.

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Books on Pain

PAIN AND ITS PROBLEMS, edited by Sir Heneage Ogilvie, K.B.E., D.M., M.Ch., F.R.C.S. and William A. R. Thomson, M.D. Philadelphia: The Blakiston Company, 1951. 194 pp. $3.00.

The editors' preface summarizes very well the main points in this book.

"Form time immemorial the problem of pain has vexed the minds of philosophers, theologians and physicians. For the physician the problem has been a relatively simple one, as, without necessarily adopting a purely materialistic outlook, he could appreciate the value of pain as a warning of disturbed function. In other words, for the physician pain subserves a useful function, for without it many a disease process would reach an incurable stage before being detected. This means that in medicine the primary problem of pain is how to assess its true significance as a diagnostic agent at the earliest possible stage. The physician, however, is a humanitarian as well as a diagnostician, and no one born and bred in the true Hippocratic tradition but has prayed again and again for some panacea which would allow him to bring relief to his patients in the throes of an agonizing pain.

"For the practitioner therefore there are three major problems of pain. In the first instance, what is the course of the pain fibres from different parts of the body to the brain? Without this fundamental knowledge, it will never be possible to find the final answer to the other two problems—the elucidation of the diagnostic significance of pain, and the alleviation of pain. This book, the latest addition to the 'Practitioner Handbook' series, is an attempt to review and re-assess the latest information on these baffling problems. Most of the chapters have already been published in *The Practitioner* as a series of monthly articles on 'Pain and its Problems,' but, in order to deal with certain aspects of the subject which were not included in the original series, several new chapters have been added.

"As the book is written primarily for the practicing clinician, emphasis has been laid upon the practical aspects of the problems, and particularly treatment. The two introductory chapters, by Professor E. D. Adrian and Dr. Gordon Holmes, provide a general review of the problem of pain by a physiologist and a neurologist who are internationally recognized as the outstanding authorities on their respective specialties. The general clinical application of these fundamental data is reviewed by Lord Moran, and the subsequent chapters deal with the problems of pain in the different systems of the body. Although this involves a certain amount of overlapping, it was felt that for the practitioner it was the most satisfactory method of dealing with the subject . . . . "

The accumulation of so much good material on pain is reflected in the contents: I. The Physiology of Pain; II. Some Clinical Aspects of Pain; III. The Meaning and Measurement of Pain; IV. Cardiac Pain; V. Pain in Peripheral Vascular Disease; VI. Pain in Respiratory Disease; VII. Pain in Disease of the Nervous System; VIII. Headache; IX. Pain in the Gastrointestinal Tract; X. Abdominal Pain; XI. Urological Pain; XII. Pain in Gynaecology; XIII. Analgesia in Labour; XIV. Pain in Rheumatic Diseases; XV. Dental Pains; XVI. Pain of Non-organic Origin; XVII. Principles of Treatment; and XVIII. The Relief of Pain in Childhood.

The book is relatively small, easy to read, well indexed and is a book that should be read by clinicians since they are constantly being faced with the problem of pain. Surely we could to advantage attempt to keep up with the progress that is being made in this field.

J.S.L.

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.*

PAIN, THE PHYSIOLOGIC TRIGGER

THE paper, "Certain Small Painful Tumors of the Extremities," by Dr. Malcolm B. Dockerty was written by special request for this issue. As readers are well aware by now, the general point of view reflected in this particular section of THE JOURNAL-LANCET concerns conditions associated with symptoms that are painful. To carry such a viewpoint even further, it was suggested that readers would gain a more definite idea of why certain lesions are painful if the histopathologic aspects of specific lesions were described. Such an understanding of the underlying pathologic factors naturally would help in the proper diagnosis of a given condition, and in preparing and treating the patient for the painful condition at hand. Dr. Dockerty has carried out this idea excellently.

Dr. Dittrich's paper on "Low Back Pain—Referred Pain From Deep Somatic Structures of the Back" deals with one of the commonest forms of pain encountered by the physician. His approach and presentation are different from those of Dr. Dockerty, yet the objectives fundamental in each paper are the same: recognition and identification of a particular symptom, pain, generally considered to be one of the most important physiologic manifestations which nature has conferred upon us. Pain is a thing, moreover, which requires the attention of both the patient and his physician, and which ordinarily will not suffer either to ignore it.

JOHN S. LUNDY, M.D.

Current Literature on Pain

LOBOTOMY FOR INTRACTABLE PAIN. JAMES L. POPPEN, M.D. and DONALD B. FRESHWATER, M.D., *Surg. Clin. No. Am.* 32: 787-789, 1952.

Though an effective procedure, lobotomy must not be undertaken lightly and in most instances should be reserved for patients with intractable pain from fatal malignant disease.

While many serious personality deficits are avoided in the unilateral or the bimedial operation, all other practical pain-relieving methods should be instituted first. The change in personality that may take place must be thoroughly explained to the family and possibility of failure stressed.

Unilateral leukotomy usually accomplishes all that is necessary and produces less personality deficit. If a second operation is necessary, the bimedial procedure is recommended. Considerably less mental aberration follows bimedial leukotomy than after the standard bilateral operation, with comparable relief.

The procedure is most efficacious in patients upset over malignant disease. In 46 patients submitting to prefrontal lobotomy, 26 were treated for relief of pain caused by malignancy. Unilateral surgery was used in 31 cases, though 8 had to be subjected to surgery on the second side. All 8 patients secured additional relief, and all but 1 of 15 bilateral lobotomies gave fair to excellent relief.

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LOCAL AND REGIONAL ANALGESIC INJECTIONS IN PAINFUL MUSCULOSKELETAL CONDITIONS. O. STEINBROCKER, M.D., *Arizona Med.* 9:27-29, 1952.

Local and regional analgesic injections are effective in many cases of intractable musculoskeletal pain until the more gradual results of therapy are achieved.

Procaine solutions are infiltrated at the site of palpable maximum tenderness, at a "triggerpoint," or about a peripheral nerve trunk to interrupt the pain circuit; in regional blocks, the paravertebral route is used to infiltrate nerves or muscles. Analgesia often continues long after the anesthesia disappears.

Relief is obtained in over 70 per cent of the cases, but success depends as much on the correct diagnosis and localization of pain as upon the analgesia. After source of pain is identified, ½ per cent procaine solution is injected at the points of maximum tenderness. No more than 5 cc. is injected at first, however, to be sure of the patient's tolerance. Since minor procaine reactions are encountered in up to 30 per cent of patients, 1½ gr. barbiturate is administered orally an hour before treatment.

In peripheral tissues, 2 to 20 cc. of ½ per cent or 1 per cent procaine is employed, and in acute traumatic lesions, three to five daily injections sometimes become necessary. In chronically-painful disorders, two injections a week suffice until improvement occurs, then once every five to seven days.

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THE MYOFASCIAL GENESIS OF PAIN. JANET TRAVELL, M.D. and SEYMOUR H. RINZLER, M.D. *Post-Grad.* 11:425-434, 1952.

Trigger areas in myofascial structures can maintain pain cycles indefinitely, but once the pain reference pattern of a muscle is known, the source of pain can be located and blocked. Effective procedures include procaine infiltration or dry needling of trigger areas, sustained heavy pressure on trigger areas, and spraying the overlying skin with ethyl chloride.

For procaine infiltration:

Demonstrate pain reference to patient by pressing on trigger area. Ask patient to announce when pain radiation is felt during infiltration. When needle hits trigger area, pepper region by moving needle in and out of muscle, injecting 1 to 2 cc. continuously. Use 0.25 to 0.5 per cent procaine hydrochloride in physiologic saline (unless history of procaine allergy). Use a sharp 22 to 24-gauge needle, 1 to 3 inches long. Apply hemostasis promptly.

Ethyl chloride spray:

Guard against fire hazards. Raise patient's head above level sprayed. Hold container 2 feet away. Start stream at trigger area, carry over reference zone. Apply stream at acute angle. Spray in one direction, with slow sweeping motion. Repeat sweeps in rhythm of a few seconds

on and off. Lengthen interval between sweeps if aching develops. Do *not* frost skin. Stretch muscle by gentle movement. Continue until pain disappears and tenderness at trigger area is less. Stop if no effect in five minutes. J.F.E.

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A CASE OF PULMONARY HYPERTENSIVE PAIN OR HYPERCYANOTIC ANGINA. Edward Balthrop, M.D., *J.M.A. Alabama* 21:249-251, 1952.

Patients presenting complaints of chest pain must be analyzed carefully because of the possibility not only of heart disease but of other conditions.

Citing a case simulating myocardial infarction but actually being pulmonary hypertensive pain, Edward Balthrop, M.D., of Mobile, Alabama, says the physician should remember three questions in analyzing chest pain: (1) Does the patient have heart disease? (2) If so, what kind of heart disease? (3) Could any other process be causing the pain?

In the case cited, history and clinical picture suggested a diagnosis of myocardial infarction with heart block, but response to oxygen and demerol in less than two hours and no temperature rise made this diagnosis untenable. Rather, signs of chronic lung disease, emphysema, erythrocytosis, hypertropic pulmonary osteoarthropathy, and hypertropic toenails, suggested the possibility that the pain arose from the lungs and not from the heart.

Four criteria warrant diagnosis of pulmonary hypertensive pain or hypercyanotic angina: (1) disorders hindering pulmonary circulation; (2) wheezing and cyanosis during seizures; (3) consistent electrocardiographic changes; and (4) ineffectiveness of nitroglycerine as compared to relief of wheezing by drugs and oxygen.

Angina probably must be present for the syndrome to occur. The site of pain is ascribed to the myocardium and cause of pain is anoxia. In addition, the amount of blood reaching the left side of the heart through the impaired pulmonary vascular bed is probably decreased, diminishing left ventricular output. Thus, coronary blood flow is impaired and myocardial anoxia enhanced.

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REDUCING PAIN IN HEMORRHOIDECTOMY. Henry E. Steadman, M.D., *J.M.A. Georgia* 61:81-83, 1952.

Stressing the importance of preoperative preparation, Henry E. Steadman, M.D., of Hapeville, Georgia, lists a procedure giving best results in obliterating pain following hemorrhoidectomy. Preoperatively, the following steps are taken: (1) hot saline sitz-baths for two to three days; (2) psychotherapy; (3) a barbiturate the night before surgery; (4) the same barbiturate 90 minutes preoperatively to relieve apprehension, produce hypnosis, and prevent possible reaction from local or spinal anesthetic; (5) a narcotic one hour before operation; (6) scopolamine; (7) a non-irritating enema of saline or, preferably, plain water 6 to 12 hours preoperatively; and (8) immediate incision of acute thrombosed external hemorrhoids.

Saddle block anesthesia, using 30 to 50 mg. of procaine or 3 to 5 mg. of pontocaine, sodium Pentothal, or curare are satisfactory anesthetics; and the Pruitt method of hemorrhoidectomy, with 20 per cent alcohol injection, is most conducive to postoperative analgesia.

Surgical methods to reduce postoperative pain should be employed, such as: (1) posterior proctotomy; (2) gentle dilation of sphincter; (3) avoidance of trauma; (4) as few sutures as possible (5) prevention of contamination; (6) tying of sutures above the area of sensation; (7) excision of blind sinuses and skin tags; (8) leaving the wound open to drain and avoiding tension on anal skin; and (9) leaving strips of mucous membrane and skin so that gaps may grow in to cover the raw areas.

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THE EFFECT OF ANTIHISTAMINES ON THE PAIN THRESHOLD: Dolorimeter Studies on Pyribenzamine and Antistine. Austin H. Kutscher, B.A., D.D.S. and Neal W. Chilton, B.S., D.D.S., M.P.H., *Am. J. Med. Sciences* 223:239-244, 1952.

Despite anesthetic properties similar to procaine, antihistamines are not able to raise the pain threshold of intact or traumatized human skin. In dolorimeter studies of 18 trained subjects, Austin H. Kutscher, D.D.S. and Neal W. Chilton, D.D.S., of Columbia University, New York City, found that a 50-mg. dose of Pyribenzamine or a 100-mg. dose of Antistine did not materially alter pain threshold. Similarly, a 50-mg. dose of Pyribenzamine had little effect on pain threshold of traumatized skin.

For 15 patients ingesting 50 mg. of Pyribenzamine, the trend of mean pain threshold throughout four hours of observation was barely significant at a 5 per cent level. In 8 patients taking 100 mg. of Antistine, the trend was not statistically significant. Five patients with skin traumatized by ultraviolet radiation ingested 50 mg. of Pyribenzamine 24 hours later, but no significant trend of mean pain threshold resulted.

While dolorimeter readings for 10 control subjects indicate that individuals differ significantly in pain thresholds, the difference between control and antihistamine-treated groups is insignificant.

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THE RELIEF OF VARIOUS TYPES OF PAIN WITH A DOUBLE CALCIUM SALT DERIVATIVE. E. L. Pollock, M.D., *J. Missouri M.A.* 49:480-483, 1952.

Intravenous injections of a double calcium salt derivative, calcium gluconogalactogluconate (Neo-Calglucon), give indications of effectiveness in the treatment of various myalgias. In a preliminary report on the compound, E. L. Pollock, M.D., of Frisco R. R. Hospital, St. Louis, Missouri, says injections of a 20 per cent solution gave complete relief to 11 patients, partial relief to 12, and failed in only 2 cases. A 30 per cent solution gave partial relief to 7 patients and failed in 1 case.

Injections are given in doses of 10 cc. after thorough examination, including laboratory tests and x-rays. The importance of diagnosis is stressed, as etiology of the pain should be determined and treated to help relieve the patient.

The use of Neo-Calglucon is based on a physiologic approach. Calcium deficiencies lead to muscular spasms, which calcium relieves. Since calcium administration increases muscular contraction, pain is probably relieved as a result of muscular relaxation.

Increase in movement and reduction in swelling and tenderness occur following Neo-Calglucon administration. Hence, in cases of sciatica, neuritis, bursitis, and lumbago, relief is discernible by the amount of normal movement that is obtainable after treatment.

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.*

Clinicopathological Conference

Minneapolis Veterans Hospital*

Edited by James F. Hammarsten, M.D.

Assisted by N. L. Gault, M.D. and Donald Fry, M.D.

Presentation of Case

A 53-year-old roofer was admitted on September 21, 1951 because of chills, fever and cough.

The patient was somewhat confused so that the reliability of the history was questioned. Six weeks before admission he was ill for one week with chills, fever, malaise, night sweats and anorexia. These symptoms subsided but he remained weak.

Three days prior to admission chills, fever and malaise recurred, and he developed a nonproductive cough. He also noted partial deafness. He had lost 20 pounds in six weeks and had not worked during that time. No past history could be elicited.

Physical examination showed an acutely ill man who was confused. He was cyanotic and the skin was flushed, hot and dry. There was dullness and decreased breath sounds at the right base. There were musical and moist rales throughout both lung fields. A grade II systolic murmur was heard at the apex. There was mild pitting edema of both legs.

The temperature was 99.8° F., the pulse rate 90 per minute, the respiratory rate 38 per minute, and the blood pressure 116 mm. Hg systolic and 70 mm. diastolic.

The hemoglobin was 13.9 gm. per 100 ml. and the white blood cell count was 5300 per mm.^{3} with 89 per cent neutrophils, 8 per cent lymphocytes, 1 per cent monocytes, and 2 per cent eosinophils. The neutrophils were described as "toxic." The erythrocyte sedimentation rate was 7 mm. in one hour. A blood Kahn was negative. The urine showed 1 plus albumin, 5 to 6 white blood cells and 3 to 4 red blood cells per high-power field and 6 to 8 granular casts.

Cold agglutinins were positive in a 1:2 dilution and plus-minus in a 1:16 dilution. A blood culture was negative. A throat culture showed hemolytic streptococci, streptococci viridans, and N. catarrhalis.

An x-ray film of the chest showed a diffuse infiltration more marked on the right. This had "the appearance of pulmonary edema." There were also nodular areas throughout both lungs. These areas "suggested bronchopneumonia or metastases" (fig. 1).

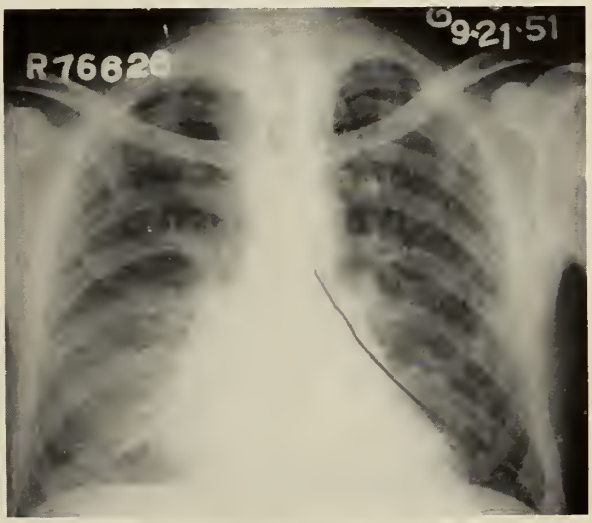

Fig. 1. X-ray film of the chest. There is a diffuse infiltration, more marked on the right.

An electrocardiogram showed an isoelectric T 1 but was otherwise normal.

He was given aureomycin orally and oxygen by B-L-B mask. His temperature rose to 105.4° F. rectally the night of admission. He remained acutely ill. He was cyanotic whenever oxygen therapy was interrupted. He remained febrile. He was seen by several consultants, each of whom suggested another antibiotic so that penicillin, streptomycin, and intravenous aureomycin were added to the therapeutic array. The patient's condition only became worse. He became semicomatose on the third hospital day. A spinal fluid examination showed normal dynamics, 1 erythrocyte and 1 leukocyte per mm.^{3}, 37 mg. sugar per 100 ml., 113 MEq. per liter chloride, and 47 mg. proteins. The blood urea nitrogen was

*Published with approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

29.7 mg. per 100 ml., the chloride 98.3 MEq. per liter, and the CO_2 21.2 MEq. per liter. The white blood cell count dropped to 3000 per mm.^{3} with no change in the differential cell count.

The temperature continued to rise to 104° F. rectally each day. The respiratory rate increased to 60 per minute. The CO_2 decreased to 16.7 MEq. per liter. On the fourth hospital day terramycin and ACTH were given and streptomycin continued. The other therapy was stopped.

On the morning of September 26 he became very cyanotic even with oxygen and died.

DISCUSSION

DR. THOMAS LOWRY*: As I read through the protocol, I looked for the signposts which would point the way to the proper path of reasoning. There aren't very many signposts. The reliability of the history was questionable; and whether reliable or not, it still doesn't add much to the situation.

We can gather that the duration of illness was six weeks. He had chills, fever, malaise, night sweats, anorexia and a high fever. These are the symptoms of a severe systemic infection. The only localizing symptom is the nonproductive cough.

The striking points on physical examination were fever, tachypnea, cyanosis, a normal cardiac shadow, rales throughout both lungs, and a systolic murmur.

The sedimentation rate of seven is interesting. Certainly a man with this sort of overwhelming toxic illness would be expected to have a very rapid sedimentation rate under ordinary circumstances. My interpretation of the low sedimentation rate is that if the infection or illness is sufficiently overwhelming there may be failure of production of fibrinogen or some other factor. I don't believe we can take it as a normal sedimentation rate in the usual sense.

The urine findings are consistent with any severe febrile illness. That no sputum is recorded I found to be a sad thing because this seemed to be primarily a pulmonary disease. The isoelectric T wave in lead 1 of the electrocardiogram is consistent with a severe toxic state.

The deviations in the blood chemistries are certainly not significant. The decrease in carbon dioxide is not surprising with a respiratory rate of 60.

The extreme tachypnea and cyanosis are of great significance. It seems fair to conclude that the lungs were literally filling up with something. With apologies to the x-ray department, I doubt whether there is a very significant amount of edema. I believe there is something in the pulmonary tissue, interstitial or parenchymal, which has caused a progressive cyanosis. The picture does not seem to be that of cardiac failure because of the normal heart size, normal blood pressure, electrocardiogram, and absence of other evidence.

We have, then, a progressive, febrile, fatal illness which is mainly a pulmonary disease. What are the possibilities?

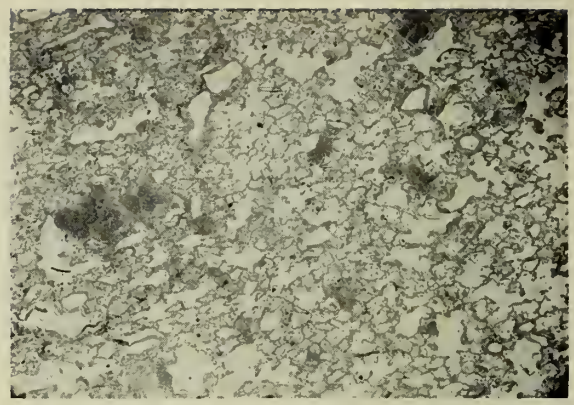

Fig. 2. Microscopic section of lung. Numerous minute tubercles are visible.

Miliary tuberculosis would be quite consistent with most of the things in the protocol. The x-ray findings aren't entirely satisfactory from that standpoint. There are certainly some tiny nodules, but not a characteristic x-ray picture for terminal miliary tuberculosis.

Another thought that occurred to me, before I had a chance to see the x-ray film, was that this might be bacterial endocarditis in the right side of the heart with multiple pulmonary emboli. That can not be entirely excluded. The systolic murmur with a normal size heart can not be disregarded although it is by no means diagnostic in the presence of severe fever.

I considered tularemia as I read the protocol, but the x-ray picture is against that. He received enough antibiotics so that if it were tularemia we should have expected some response.

Other things I considered were staphylococcic pneumonia, histoplasmosis, Hodgkin's disease, and metastatic carcinoma.

My first choice is miliary tuberculosis, involving primarily the lungs.

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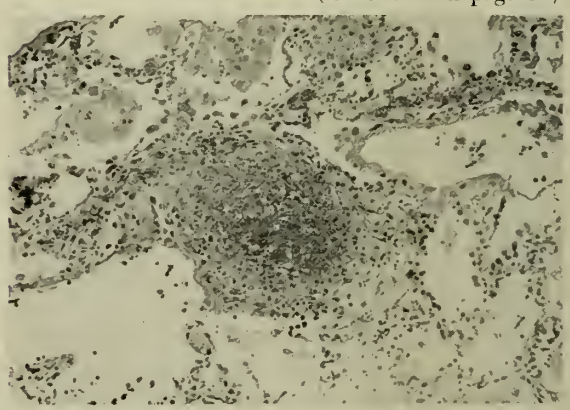

Fig. 3. Microscopic section of lung with greater magnification than figure 2. One tubercle is seen. There is no evidence of fibrosis or epithelioid cell reaction.

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Lancet Editorial

The Future Relationship of Physiology to Clinical Medicine and Surgery*

Physiologists could improve their role as teachers through a more intimate acquaintance with the solution of day-to-day problems in the clinic.

Physiologists are accustomed to predict what would happen, given a certain set of conditions, but they are not so well prepared to reason backward from a certain result and suggest what the conditions were which brought that situation about.

Over a period of ten years, through the co-operation of Dr. Maurice B. Visscher, chairman of the Department of Physiology in the Medical School of the University of Minnesota, a weekly physiologicosurgical conference, participated in by the staffs of both the Departments of Surgery and Physiology, has been held in one of the lecture halls in the University Hospitals for the discussion of problems of current interest to the surgeons. These ventures have been of enormous help to the surgical staff. Out of these discussions have come many helpful suggestions for attacking pressing problems—suggestions which, in many instances, have turned out to be research projects and have come to occupy the attention of the staffs of both departments in their respective laboratories. The continued interest of the staff of the Department of Physiology in these conferences over this long period indicates definitely that they find them profitable too. For the undergraduate as well as the graduate student, they probably provide the best teaching which the Department of Surgery has to offer.

Will the time ever come when medical and surgical services will avail themselves of the help of the physiologists in the wards The time is overdue for more active participation by physiologists as consultants to clinical services in teaching hospitals. Such a development could become a tremendous boon to clinical medicine. I think that physiology would profit equally thereby. Discussions before the American Physiological Society in 1946 and 1947 suggest that some physiologists entertain rather pessimistic views with reference to the future of physiology. Physiologists probably are needed in industrial research and to enliven the teaching of biology in the smaller colleges, but an outlet which should prove more interesting to the physiologist and afford him a more satisfactory place to work would be the teaching hospital. The first question to be raised by such an arrangement, of course, is who will supply the laboratory and support the undertaking? With a meeting of the minds, however, such a co-operative venture should get off to a promising start. In consequence, there might come to be two groups of physiologists—the experimentalists in general physiology as now, and an equally important division, whose members would spend a definite, if not a major, portion of their time in the wards and laboratories of teaching hospitals. The latter group of physiologists should be doctors of medicine too, I believe. Eugene Landis, at Harvard, has shown the value of the human subject for demonstration of laboratory procedures. Could not certain procedures be taught in the ward with the physiologist having simultaneously an eye to the improvement of technics which would redound to the benefit of the patient Physiologists have machine shops for the development of tools necessary in the prosecution of their experiments. Why not machine shops in which the physiologist may develop precision instruments for the study of disease and its care in man?

What if physiology did become the handmaiden of medicine? Would physiology suffer? I do not think so. On the contrary, if the physiologists could be given actives roles in the wards of teaching hospitals, I believe that presently physiology would assume and maintain a role in medicine equal in importance to that enjoyed by pathology during its years of ascendancy. Are we not all servants of society? Has clinical surgery swallowed up the academic surgeon? No, academic surgeons have multiplied, and society as well as surgery, have gained in the process.

I am not suggesting that the physiologist give up entirely the seclusion of his laboratory for a burst of energy in the wards. However, at least a few housewives must give thanks every day for the preoccupation afforded by small but useful tasks. Some of the surgeon's work like some of the housewife's borders on the dull. However weary he may become occasionally by the irksome tasks of the cut-and-tie maneuvers, in effecting hemostasis in operations I do not believe that I am wrong in suggesting that most surgeons are grateful for these engrossing aspects of their labor. Who can spend all his time profitably under the heat of the intellectual forge?

Part of the problem involved can be bridged by sending budding surgeons of promise to the physiologist for a year or two, when the end of the training period in surgery is in sight.

Anatomy was formerly the stepping stone to surgery as pathology was for the internist. Today physiology and biochemistry appear to be supplanting anatomy and pathology in the training of surgeons as well as internists, who are anxious to acquire the knowledge and technics of another discipline as research tools in the furtherance of their careers. This departure has become standard practice in the training of career surgeons in the department of surgery with which I am identified. It has been a rich and rewarding experience for the men concerned as well as for the department as a whole. However, I have the feeling that more active participation by physiologists in some of the problems of clinicians would do far more than complement the program of sending surgeons to physiologists for a portion of their training. It

(Continued on page 81)

*Reprinted from Proceedings of the Staff Meetings of the Mayo Clinic, December 17, 1952. Vol. 27, No. 26.

Diseases of the Nervous System in Infancy, Childhood and Adolescence, by Frank R. Ford, 1952. Third edition. Springfield, Illinois: Charles C Thomas. 1180 pages. $18.50.

In considering a book as comprehensive and as well-known as this one, it is customary for reviewers to emphasize the importance of the book, its detailed coverage of a wide range of subjects, and its value to certain professional groups—in this case the pediatricians and the neurologists particularly. Cetrainly these things need to be said about the third edition of Ford's *magnum opus.* In no other work will be found the detailed and authoritative coverage of the many aspects of pediatric neurology.

Inevitably in a work as large as this almost anyone will find that some subjects are handled less well than others. The present reviewer found the discussion of poliomyelitis to be "orthodox" to the point of being doctrinary. Immobilization of affected extremities is still advocated. The clinician will find little of help regarding treatment. The subject of meningitis receives a curiously uneven treatment with scarcely a page being devoted to influenzal meningitis, which is such an important variety in pediatries. Many of the recommendations made regarding the treatment of meningitis are not in accord with the best current practice. A short section on disorders of speech and language is evidently included only for the sake of completeness, and contains many serious errors. On these problems and certain others (e.g., congenital megacolon) which likewise are usually not handled by the neurologist, the author has not bothered to become acquainted with the best current theory and practice.

These defects can easily be forgiven, however, for one rarely turns to a book on pediatric neurology to learn how to treat meningitis. One may often consult it for help in diagnosis and treatment of many other types of problems, however—developmental defects, degenerative disorders, neoplastic and vascular diseases. He may wish assistance regarding the effects on the nervous system of diseases of other organ systems. On these matters and many others Dr. Ford speaks with assurance, and the many virtues of his book outweigh its occasional imperfections.

The Treatment of Injuries to the Nervous System, by Donald Munro, M.D., 1952. Philadelphia: W. B. Saunders Company. 284 pages. $7.50.

In these days when so many hundreds of badly injured soldiers are being flown quickly from the front to a base hospital, neurosurgeons are having to develop new skills in the handling of persons with severe brain and cord and nerve injuries. The book has been written, however, for the use of the general surgeon and the use of the general practitioner because they often have to deal with these cases. They may have to inherit and take care of some paraplegics. Oftentimes the general surgeon or the general practitioner is the first to see the boy who gets a broken back. Up till now these non-specialists have been greatly handicapped in their work by the lack of any concise book dealing with these problems.

Current methods in use in the author's neurosurgical clinic in the Boston City Hospital are described. There is a fine chapter on the cost of the medical care of paraplegics, and how it may be modified by rehabilitation services.

Every medical man who has to deal with the badly injured man will be tremendously helped by the information supplied by this book. It will help him in carrying the patient from the first shock of injury up to the rehabilitation, and the getting around on artificial limbs.

W.C.A.

•

Chronic Ulcerative Colitis, by J. Arnold Bargen, M.D., 1951. Springfield, Illinois: Charles C Thomas. 59 pages. $2.00.

This monograph deals with the form of ulcerative colitis designated by the author as "thrombo-ulcerative (streptococcal) colitis." With this premise in mind he discusses the pathology, the diagnosis, the complications and the treatment. The principles outlined are, however, applicable to any form of ulcerative colitis with perhaps the exception of the acute fulminating type. This monograph should serve as a handbook for both students and practitioners who are called upon to treat an occasional case of ulcerative colitis. The monograph is well written and well outlined. W.P.E.

•

Post Graduate Lectures on Orthopedic Diagnosis and Indications. Vol. IV, by Arthur Steindler, M.D., F.A.C.S., 1952. Springfield, Illinois: Charles C Thomas. 318 pages, 338 illustrations. $9.75.

The fourth and final volume of the author's distinguished series on orthopedic lectures and diagnosis has recently become available for perusal. Similar to previous editions the main structure of this book is concerned with two principal topics. In this instance the arthridites along with the many associated diseases are discussed in their relationship to orthopedic surgery. The second portion of the book is focused on the sundry manifestations of the deficiency and degenerative disease of the locomotor system.

The usual overwhelming information that must be regarded with any dissertation related to arthritis has been carefully dissected so that the reader has little difficulty absorbing the opinions expressed.

It is this unique ability of the author to present his subject matter with a minimum of extraneous discourse that affords the feeling of close personal contact distinguishing the entire effort. The disclosures are motivated from a thirty year background of clinical experience and as such are proffered in an aura of judicious clarity. That some of the opinions will pass without debate is unlikely, perhaps, even impossible. Nonetheless the great majority of the information is readily accepted as dogmatic orthopedic guideposts.

The context is conveyed in lecture form with the orderly presentation of a well prepared didactic discussion. Whenever necessary radiographic reprints and photomicrographs are available for more accurate definition. In addition a well organized bibliography follows each chapter for those who may desire to investigate the subject further.

This fourth text, along with its predecessors, fulfills one of the great recent contributions to the study of orthopedics. It is worthy of highest recommendation. E.H.O'P

American College Health Association News . . .

Dr. John P. Monks, chairman of the New England Section, gives the following report of the annual meeting of his section:

The meeting was called to order by chairman John P. Monks December 6, 1952 in the Recreation Building on the Wellesley campus, with forty-two college physicians and nurses present.

Dr. John Ewell of Yale University was unanimously elected chairman for the year 1953. It was agreed later in the meeting that an early December meeting should be held in 1953.

It had been decided to center the meeting informally around a few topics which were of concern to the current development of policies of the National Association, particularly: (1) the formulation of a specific current concept of health education in a college or university; (2) the qualities necessary in a student health physician; (3) the training of college health physicians; (4) the place of research in a college health department.

In reference to *health education,* Dr. Rogers (Yale) spoke of the difficulties in developing methods for communicating health information to students. One is frustrated by the "total nonchalance" of most students. Dr. Bock (Harvard) spoke of the necessity of convincing faculty members of newer concepts of the care of health in the face of tradition. (It is of interest that the "hygiene lecture" was scarcely mentioned, the opinion of the group favoring education by individual conference.) Dr. Radcliffe (University of Massachusetts) mentioned a health council containing faculty members which served initially in the formation of policies in his department. The importance of the physician taking time to explain matters to the student patient and of liaison with the faculty were stressed.

In respect to the *kind of doctor to take up student health work,* Dr. Hardy (Massachusetts Institute of Technology) suggested that he should have some experience in general practice. Other ideas along this line were that he should not be a "prescription reflex" doctor; he should have interest in the person, in the moral and living qualities of the person as well as the physical well-being. Dr. Farnsworth (Massachusetts Institute of Technology) distinguished between physicians who thought in terms of health from those who thought in terms of disease. Several physicians spoke of the differences between large and small institutions in their requirements, and the fact that the organization of departments might vary markedly from one college to another.

In speaking of *training of young college health physicians,* Dr. Farnsworth advocated a dozen or so places throughout the country which would plan definite ways of undertaking training in student health, possibly giving fellowships to men just out of residency. Massachusetts Institute of Technology is endeavoring to give the trainee experience in all aspects of the department, including organizational matters, psychiatric techniques, counseling, personnel and morale problems.

With regard to the *place of research in a college health department,* Dr. Heath (Harvard) described briefly the Grant Study as an example of the endowed research center associated with a student health department. He spoke of the value of prolonged follow-up. The special fields of the study—psychiatry, psychology, physiology, medicine, physical and cultural anthropology—represent different ways of studying the individual and bring into the study cooperative use of various departments of a large university. Dr. Farnsworth and Dr. Means went into some detail in describing a faculty health survey at Massachusetts Institute of Technology. Out of a faculty of 490, nearly 300 volunteered to take part since the start of the study a year ago. They underwent a complete medical examination and in addition psychiatric interviews. Each subject was discussed later in group conference and given a report. Perhaps less than the expected amount of disease was discovered. Hypertension was less than expected. Peptic ulcer was the most common chronic condition. The fact that faculty members were seeing psychiatrists tended to remove the stigma of "seeing a psychiatrist" from the student's mind.

Dean Lucy Wilson of Wellesley spoke to the group in place of President Margaret Clapp, who sent her regrets that she could not be present because of illness.

* * *

There are three college physicians, four college nurses, and one secretary-laboratory technician on the staff of the Radcliffe College Health Center. They are as follows: Barbara Campbell Gurd, M.D. (Mrs. Campbell Gurd), college physician in charge of administration; Helen N. Perry, M.D. (Mrs. Reginald Perry), college physician; Dorothy MacLeod, M.D. (Mrs. John McLeod), college physician; Sallie Fitch Moore, R.N., head college nurse; Mary A. Perry, R.N., assistant college nurse; Ruth A. Callahan, R.N., assistant college nurse; Henrietta Bonheyo, R.N., part-time college nurse; Barbara Phillips Christian, R.N. (Mrs. J. Richard Christian), secretary and laboratory technician.

* * *

A position is available for a qualified physician in the Student Health Department of a large eastern university with an active clinical program. Arrangements could be made for either a nine month appointment or a twelve month appointment with one month's vacation. In case of the latter, the salary would be $8,500 to start. All those interested in this position, please apply through the secretary-treasurer of the American College Health Association, Edith M. Lindsay, School of Public Health, University of California, Berkeley 4, California.

* * *

The Executive Committee met in Chicago during the Christmas holidays. Present were: Max Durfee, M.D., president; Dana L. Farnsworth, M.D., president-elect; Leona Yeager, M.D., vice-president; Edith Lindsay, secretary-treasurer; and Irvin W. Sander, M.D., past president. William T. Palchanis, M.D., a member of the program and local arrangements committee, was also present.

The first order of business was the discussion of the program and arrangements for the annual meeting. A number of stimulating and pertinent papers are being prepared for your enlightenment. Now is not too early for you and members of your staff to make plans for attending the meeting scheduled for April 30, May 1 and 2 at Columbus, Ohio. You will receive a preliminary program in March.

The Executive Committee also discussed the proposed training program for physicians developed by Irvin W. Sander, M.D., chairman. Dr. Sander will give you information about the program next month in this column.

News Briefs . . .

North Dakota

Dr. John H. Moore of Grand Forks took part in a round table discussion at the annual meeting of the American Academy of Obstetrics and Gynecology at Chicago on December 16.

* * *

The program of treatment for the cure and control of alcoholism was discussed at the December 21 meeting of the subcommittee of mental health of the North Dakota State Medical Association held at State Lodge. Dr. James Holliday of Kenmare is chairman of the subcommittee.

* * *

Dr. E. T. Bell, professor emeritus in pathology at the University of Minnesota, lectured to sophomore medical students at the University of North Dakota at Grand Forks on December 17. He also attended a clinical pathological conference on kidney disease problems at Deaconess hospital, spoke on cancer research at the University, and attended the evening meeting of the Grand Forks District Medical Society at the Dakota Hotel.

* * *

The completely remodeled building of the Harvey Medical Center had its formal opening recently. Doctors associated with the center are A. F. Hammargren, C. J. Beck, Lowell Boyum and F. W. Ford.

Minnesota

According to recent figures, a total of 3,891 persons in Minnesota were victims of poliomyelitis during 1952. Although there were 1,000 more total cases than in 1946, the last record year, there were fewer deaths than in that year. In 1952, 198 persons died of polio, and 226 during the 1946 outbreak.

Olmsted county was the hardest hit area with 12 deaths and 208 cases in a population of 48,200. Hennepin county had 977 cases with 46 fatalities, while Ramsey recorded 375 cases and 18 deaths. No cases were reported from Cook, Kittson or Red Lake counties—all in the northern part of the state.

Dr. Frederic Kottke, head of the division of physical medicine at the University of Minnesota, estimates that about 600 of these 3,891 polio patients will need some sort of physical rehabilitation, and about 350 to 400 will need prolonged treatment.

* * *

Dr. Albert J. Chesley, executive officer of the Minnesota state board of health for nearly 30 years, was one of the Town Toppers featured in the Minneapolis *Star* of January 6.

* * *

Dr. Samuel F. Haines, Rochester, was elected chairman of the board of governors of the Mayo clinic to succeed Dr. Arlie R. Barnes who resigned because of illness. A graduate of Harvard university medical school in 1919, Dr. Haines came to the Mayo clinic in 1921 and became a staff member October 1, 1924.

* * *

Dr. W. D. Brodies was elected chief of staff of St. Luke's hospital, St. Paul. Chief of staff-elect was Dr. D. L. Martin, and secretary, Dr. John V. Farkas. Other officers include Dr. Victor P. Hauser, chief of surgery; Dr. E. J. Black, chief of medicine; Dr. J. S. McCabe, chief of obstetrics-gynecology, and Dr. J. W. Edwards, chief of general practice.

Proceeds from the "Holiday on Ice" held at the St. Paul auditorium on January 4 went to the Diagnostic Clinic for Rheumatic Fever, which serves St. Paul residents under 21 referred there by their doctors. Dr. John Calligan is medical director of the clinic.

* * *

Dr. John Boehrer was elected chief of staff of Abbott hospital, Minneapolis, at a meeting on January 6. Other officers named include Dr. John Pewters, vice president, and Dr. John Tobin, secretary.

South Dakota

dr. j. russell brown, Watertown, has been named to a five-man committee to advise the board of trustees of the American Medical Association. Dr. Brown has been the South Dakota delegate to the association for the past five years.

* * *

dr. robert s. anderson, professor of physiology at the University of South Dakota medical school, will take part in a symposium sponsored by the Faraday Society at Cambridge, England. The subject of the symposium is the chemistry of biological aftereffects of ultraviolet and ionizing radiations.

* * *

dr. joseph n. hamm of Sturgis was elected president of the Black Hills District Medical Society at their meeting on December 11. Also elected were Dr. Arthur Semones, Lead, vice president; Dr. H. J. Grau, Rapid City, secretary-treasurer; and Dr. G. S. Owen, Rapid City, censor. The society voted to establish annual freshman nursing scholarships for the South Dakota State College department of nursing education, Brookings, and St. John's School of Nursing at Rapid City. The annual awards will be given girls from the Black Hills region.

* * *

dr. frank w. hass has resigned as superintendent of Yankton state hospital after serving there for the past twenty-five years. He plans to enter private practice in psychiatry in Yankton.

* * *

dr. wayne gieb, Rapid City, has accepted the position of chairman of the medical division of the defense council at Pierre. He replaces the late Dr. Donald Slaughter of Vermillion.

* * *

dr. robert p. masland, jr., a graduate of the College of Physicians and Surgeons, Columbia University, has joined the staff of the Yankton clinic in the department of internal medicine.

Deaths . . .

Dr. L. J. Seibel, 60, of Harvey, North Dakota, died December 7. A graduate of the University of Minnesota medical school in 1931, Dr. McClusky had practiced at Harvey since 1932.

* * *

Dr. Asa J. Hammond, 83, Minneapolis, died December 19. He was a graduate of the University of Minnesota medical school in 1896, a member of the A.M.A., Hennepin County medical society and an honorary staff member of St. Barnabas hospital.

* * *

Dr. Karl C. Wold, St. Paul, died Wednesday, December 24.

MEDICINE IN GREAT BRITAIN
(Continued from page 46)

ings were to be held, but that the representatives themselves would discuss that acceptance of invitations. Interestingly enough, this resolution was soundly defeated, not because of the eloquence of the man who was an opponent, but because they were generally fed up with centralization.

I found it necessary to leave after a period of listening to "an attempt at adjustment with the government" which discussion brought about nothing specific except to indicate by inference that the physicians were still out in the cold. Scientific meetings were very good, certainly on a par with anything we have in the United States. However, this was the first meeting in which they had had scientific exhibits as patterned after us, and the physicians welcomed this markedly. In general it was a worthwhile convention.

The meeting at Nottingham brought about the question of health education. I was disappointed to see so many of the men take the "hands off" attitude. However, the radio, magazine and newspaper problem there does not compare with that in the United States. They have few of the lay medical articles which cause us all so many headaches. Again, as is typical of the British reserve, many felt it best not to tell the patient or student too much. Hopefully many others agreed with us that the education of the public aids the physician and improves medicine. Their progress in this direction is considerably behind us.

In conclusion I should like to say that we can learn many things from Britain, not only from its contributions, but from its mistakes. Only briefly have I outlined the many factors observed; each could be elaborated with more facts and findings.

A CONTROLLED CLINICAL EVALUATION
OF TWO HEMATINIC AGENTS
(Continued from page 56)

ority of I.S.M. over ferrous sulfate in regard to tolerance has not been measured with a completely satisfying degree of quantitativeness in this study. All that can be said is that the superiority of I.S.M. in this regard is very real. As a corollary of this observation, it is interesting to note that the surplus of I.S.M. tablets on hand at the conclusion of this study has long been exhausted, whereas the over-supply of ferrous sulfate tablets remains apparently unwanted. It should also be reported here that the better tolerance to I.S.M. medication reported in this study is in complete harmony with that observed in previous clinical studies.

SUMMARY

A clinical study has been conducted in which a new complex iron salt (iron sodium malate) in combination with certain adjuvant substances* has been compared with ferrous sulfate.

Including controls, the study involved a total of 265 patients selected from a total of over 1200. Attention was focused on three distinct population groups: juvenile, prenatal and geriatric; and each group consisted of sufficient medication and control patients to permit statistical analysis of the data.

In order to obtain data of practical significance, patients selected for participation were those for whom oral iron would constitute the only indicated therapy. Initial hemoglobin levels were therefore on the order of 75 to 80 per cent of normal.

The combined data for all patients shows that the response to the iron sodium malate medication is greater and more rapid (less lag) than that to ferrous sulfate. These findings were especially evident in the juvenile and prenatal groups.

Evaluation of side-effects, both favorable and unfavorable, resulted in an overwhelming preference for the iron sodium malate medication.

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*Supplied as Irocine.

CLINICOPATHOLOGICAL CONFERENCE

Minneapolis Veterans Hospital

(Continued from page 72)

DR. STEAD: I would like to inquire about the low carbon dioxide. He was cyanotic even with oxygen administration. Now if that was due to poor diffusion I should think he should also have trouble getting CO_2 out.

DR. EBERT: If there is a shunt through abnormal pulmonary tissue, you may see exactly this picture. The remaining ventilated lung may lower the carbon dioxide tension in the blood, and as a result of blood shunted through nonventilated alveoli the oxygen saturation may be low. This is the finding in severe lobar pneumonia.

The clinical diagnosis was acute bronchiolitis. The reason we considered that diagnosis was that we had seen two other patients with similar clinical picture and acute bronchiolitis. They had almost pure cultures of Hemophilus influenza bacilli from the sputum.

DIAGNOSES

Clinical diagnosis: Acute bronchiolitis.

Dr. Lowry's diagnosis: Acute miliary tuberculosis involving primarily the lungs.

Anatomical diagnosis: Acute miliary tuberculosis.

PATHOLOGICAL DISCUSSION

DR. GLEASON: A sputum obtained shortly before death but reported later showed tubercle bacilli and the spinal fluid culture also showed tubercle bacilli.

There was 2000 cc. of bloody fluid in both pleural cavities. The left lung weighed 1580 gm. and the right 1700 gm. Both lungs contained discrete white nodules averaging about 1 mm. in diameter (fig. 2). The lungs were edematous. The spleen weighed 425 gm. Microscopical examination showed myriads of minute miliary tubercles in almost every organ. The prostate, kidneys, pancreas, spleen, thyroid, liver, lymph nodes, adrenals, bone marrow, urinary bladder, and lungs were involved. There was no evidence of either fibrosis or epithelioid cell reaction (fig. 3). The probable focus for the hematogenous spread was a bronchial lymph node in which there were epithelioid cells, fibrosis, caseous necrosis, and calcification.

LANCET EDITORIAL

(Continued from page 73)

would accelerate momentum toward making the practice of surgery more physiologic. The clinic is in great need of what the physiologist has to offer, even though the invitation has not yet been generally sounded by the clinicians.

Although not pretending to affect the role of even a minor surgical prophet, I venture to predict that presently a weekly physiologicosurgical conference, in which the complex problems of the living patient are presented, will supersede the clinicopathologic conference in importance for the instruction and orientation of the surgical staff in university clinics.

OWEN H. WANGENSTEEN, M.D.,
Professor of Surgery,
University of Minnesota

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The Diagnosis and Treatment of Acute Cerebrovascular Lesions

ALLAN A. BAILEY, M.D.*
Rochester, Minnesota

THE diagnosis of a cerebrovascular accident or acute hemiplegia in many cases seems satisfying and simple. The terms, however, sometimes are used without careful consideration of either the cause or location of the lesion. It is apparent that not all patients with acute hemiplegia prove to have vascular lesions, and furthermore not all vascular lesions occur in the cerebrum. Even within the bounds of the term "vascular," several different causes must be considered.

A general practitioner, during a consultation late at night, turned to me and remarked, "All my atypical cerebrovascular accidents have turned out to be brain tumors." This is a good working point of view for any physician. We shall try to develop it by illustrating the need for clarity of thinking in regard to the subject of acute cerebrovascular accidents.

Every effort should be made to identify the location and cause of the lesion. The clinical method is the only reliable one, and cannot be passed by in favor of electroencephalography or pneumoencephalography. Inquiry about antecedent symptoms, illnesses and injury to the head is important. For example, a history of headache or personality change, progressive hemiparesis or focal seizures may point the investigation in the direction of search for a brain tumor. Antecedent illness such as heart disease of any type, blood dyscrasia, carcinoma or infectious processes may give the clue to quite another type of cause for the so-called cerebrovascular accident. Mention of such diseases in differential diagnosis will call to mind the possibilities of cerebral embolism, specific causes of cerebral hemorrhage or thrombosis, intracranial metastatic lesions and brain abscess.

Patients who have brain abscess are not seen so commonly as they were in the days before chemotherapy and antibiotic agents, when intracranial extension of a septic process from ears or sinuses was common. Brain abscess may be initiated by an embolus arising from a septic focus in the lung or in fact any part of the body.

A history of injury to the head in the two to three months prior to the time of consultation may require careful evaluation, even when the patient is aged, with evidence of diffuse vascular disease and co-existing hypertension. Intracerebral hemorrhage, subdural hematoma, brain tumor and brain abscess usually give similar signs of increased intracranial pressure in patients, but distinction from a so-called cerebrovascular accident may not be easy.

The important signs of increased intracranial pressure are the presence of deep quiet coma, fluctuations in the depth of coma, papilledema, a slow pulse or progression of the symptoms. Of these signs, papilledema often is the absent one. The incidence of neurosyphilis in the population

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varies greatly in different localities, but the disease should not be forgotten as a possible cause. The methods of establishing such a diagnosis are well known. Among young people multiple sclerosis should be thought of in the differential diagnosis of acute hemiplegia or hemiparesis.

In considering the various causes of acute cerebrovascular lesions, the physician usually thinks of thrombosis, hemorrhage and embolism. Cerebral embolism occurs rarely, and need not be seriously thought of in the absence of endocarditis or auricular fibrillation. The onset of symptoms is sudden, or, on the other hand, there may be no signs or symptoms unless an embolus involves an important artery.

The incidence of cerebral hemorrhage in comparison with that of thrombosis in practice is difficult to ascertain. No one knows how often thrombosis in a vessel may precede hemorrhage. In the past, too much emphasis has been placed on the history of a sudden onset in the case of hemorrhage. This by itself is an unreliable point, and even the presence of blood in the cerebrospinal fluid may be misleading unless the fluid is grossly bloody. Syncope at the onset, severe headache, vomiting, convulsions, deepening coma, rigidity of the neck and blood in the cerebrospinal fluid almost certainly indicate an intracranial hemorrhage. The presence of two of these signs may be enough to permit distinction between cerebral hemorrhage and thrombosis.

In a general way, in patients less than 60 years old, intracerebral or subarachnoid hemorrhage is more common than thrombosis. The presence of hypertension in a patient of this age group is a point in favor of hemorrhage. Among persons more than 60 years of age, and especially in the absence of hypertension, cerebral softening is a more likely cause. In young people, and not infrequently in older patients, a history of a sudden severe headache with or without syncope should bring to mind subarachnoid hemorrhage secondary to the rupture of a congenital aneurysm as a cause of the symptoms. Coma of varying degree and rigidity of the neck, rather than hemiplegia, may be the outstanding signs in such patients. Spinal puncture may clarify the diagnosis. The fluid is found to be grossly bloody, in a few days may be xanthochromic, and in seven to ten days may be clear, if the patient is improving. In the case of intracerebral hemorrhage, the cerebrospinal fluid may be clear or contain only a few erythrocytes.

As to spinal puncture, there is no need to be in a hurry to do it. It certainly should not be performed until the examination is complete, and a complete examination obviously includes ophthalmoscopic examination. If papilledema is present, spinal puncture is contraindicated. In the presence of a suspected intracranial lesion, performance of Queckenstedt's test is not indicated and may be dangerous.

The foregoing remarks have concerned problems of determining the cause of disturbed intracranial function. The next point to consider is how to localize the lesion. Every physician has been taught at least the rudiments of neurologic examination and neuro-anatomy. However, there always seems to be some diffidence about applying this knowledge. Furthermore, there is a tendency to neglect the details of a complete examination because the patient is semicomatose or the diagnosis looks simple. Patients who have intracranial disorders are not always easy to examine, but this is no reason for giving up before every effort has been made to obtain the best possible cooperation of the patient. It is not enough to state that the pupils are equal and react to light, that there is no voluntary motion in an extremity and that the sign of Babinski can be elicited.

Examples could be given of patients who would illustrate the value of a more detailed examination. In any case, we make a plea for the use of more detailed examinations. The patient should be observed for a few minutes before questions are asked and actual tests are attempted. His position in bed, his movements, his breathing and any spontaneous remarks should be noted. Palpation and auscultation of the cranium, and examination of the ocular fundi, cranial nerves, including the visual fields and motor power and tone, are important. Actually, the time-honored examination of reflexes may be less important than the sensory examination, with particular reference to pain and joint sensation. Tests of coordination are often possible, although they seem to be neglected. Stiffness of the neck and Kernig's sign may be present. Tests for aphasia and an appraisal of the mental status are of great importance. When these things have been done, the routine laboratory work, roentgenograms of the head, electroencephalographic study and spinal puncture may be considered.

The problem of localization in the case of suspected vascular accidents will be considered next. It is true that the most common site of occurrence of a vascular lesion is the internal capsule, and the vessel involved usually is the middle cerebral artery or its branches. When

very extensive lesions occur, hemiplegia, complete hemianesthesia of body, limbs and face, and homonymous hemianopsia on the side opposite the lesion may be found. These signs also are found if occlusion of the posterior cerebral artery has taken place; in addition, palsy of the third cranial nerve may be present. If there is no evidence of palsy of the third cranial nerve, it may be very difficult to distinguish between occlusion of the middle cerebral artery and occlusion of the posterior cerebral artery. In a general way, the farther back the site of the lesion is, the less the degree of hemiparesis will be, and the greater the evidence of hemianesthsia or hemianopsia will be. If the lesion is situated farther forward, the more likely sign will be hemiplegia of a spastic type. In lesions of the left side in right-handed patients, there will be, in addition, signs of expressive aphasia if the lesion is anterior. Defects in recognition and comprehension are more prevalent when the lesions are situated farther back.

Lesions of the brain stem have been described under a series of eponyms. The number of eponyms increases as time goes on, and multiplies the difficulties of understanding the problem. There is something ludicrous about listening to physicians argue about whose name should be applied to a syndrome. It would be much better to use a term which would name as accurately as possible the location of the lesion and would consider its probable nature. When we speak of thrombosis of the basilar artery, we tend to think of complete occlusion of this vessel, rather than partial occlusion or occlusion of some of its branches. Lesions of the upper part of the pons and midbrain as a rule give evidence of palsy of the third nerve, dysarthria and varying degrees of hemiplegia, hemianesthesia and incoordination, depending on the extent and location of the lesion. Unconsciousness is a likely accompaniment, and even decerebrate rigidity may occur in some instances. In lesions situated lower down, dysarthria, nystagmus, palsy of the sixth cranial nerve, and paresis of one, two, three or four extremities are common signs. In the presence of midpontine lesions nystagmus and dysarthria are likely to be more evident signs than palsy of the sixth cranial nerve.

It is easy to visualize that palsy of the sixth and seventh cranial nerves, with contralateral paresis and anesthesia, is likely to occur when lesions of upper part of the medulla and lower part of the pons are present. As the site of the lesion descends still further, palsy of the tenth and twelfth nerves makes its appearance. In occlusion of the anterior inferior cerebellar artery, ataxic gait and perhaps complete deafness on one side are to be found.

The syndrome of a lesion of the posterior inferior cerebellar artery warrants some elaboration. Sometimes it is called the "syndrome of the lateral medullary angle." The eponym is "Wallenberg's syndrome." As occurs in many of the lesions involving pons or medulla, the illness begins with acute dizziness, nausea, vomiting and ataxia without loss of consciousness. The astute patient realizes that one side of his face feels numb, and that the other side of his body feels numb. Sensation of pain and temperature is the only modality affected. Slight ipsilateral hemiataxia and slight contralateral hemiparesis may be present. Occasionally, diplopia and Horner's syndrome may be observed. If the disturbance is caused by thrombosis, the prognosis is good, apart from persistent pain over the face and the development of trophic corneal ulcers in a few patients. The prognosis in the presence of hemorrhage is more serious. Lesions of the vertebral arteries are rare and serious. The symptoms of thrombosis of the anterior spinal artery should be considered in a discussion of another subject.

TREATMENT

The following remarks deal with treatment during the first or second week of the illness of the patient who has an acute cerebrovascular lesion. There are no specific measures of treatment, but there are some important aspects of symptomatic treatment. It seems unlikely that the early enthusiasm of certain investigators for medicinal or mechanical methods of producing intracranial vasodilatation to alleviate the symptoms of cerebral infarction will be substantiated. Negative reports are always slow to appear in the literature, even though many workers have come to such conclusions. Actually, the great value derived from attempts to produce vasodilatation has been the emphasis on further research in this important field, and on more detailed attention to general measures of treatment.

The patient needs attention, management and encouragement. These things are provided by attention to the following details. Especially desirable is attention to those details which produce the comfort the patient may be unable to ask for. The physician is responsible for supervision of such details. Precautions to prevent the patients from falling out of hospital beds are always necessary. In the home, where beds are lower than in the hospital, such precautions

may not be necessary. Moderate elevation of the head of the bed is advisable.

Many patients, for a variety of reasons, need to be fed by someone. This is a time-consuming task, requiring much patience on the part of the attendant or nurse. Nurses experienced in the management of older patients handle this problem well, but the physician needs to give instruction and demonstrations of the technic to the novice. If the patient cannot swallow, feeding by tube after the first day or two is a more satisfactory method of providing nourishment than the use of intravenous infusions. Small quantities of liquids and food should be given frequently. The patient must be turned at regular intervals, the bed must be kept dry and clean, and the sheets unwrinkled.

Attention to the patient's bladder and bowel is necessary. Marked restlessness in a dysphasic or semicomatose patient often means that a distended bladder is the offending irritant. Incontinence or dribbling may suggest this problem in older patients, and an indwelling catheter may be necessary to abate this symptom. The use of a mild laxative agent occasionally will prevent impaction and serious constipation. It is wise to treat this problem early, and thus to prevent the patient's straining on a bedpan, an action which may lead to further intracranial hemorrhage. It should not be forgotten that watery diarrhea with incontinence may take place in the presence of an impacted rectal fecal mass.

Insomnia occasionally is a problem. It may be difficult to manage in a confused, disoriented patient. Sedatives and hypnotic agents usually fail to relieve the symptoms adequately. Old people tolerate barbiturates and bromides poorly. An ounce and a half of whisky may be tried at bedtime. Chloral hydrate in doses of 10 to 20 grains in solution is a good sedative. However, it must be emphasized that sedatives are a poor substitute for the use of things which make people comfortable and which produce a setting conducive to sleep.

The vegetative functions having thus been cared for, attention should be directed to management of the psychologic problems. Explanation to the patient and relatives of the many facets of the illness is very important. This may have to be done repeatedly, day after day. The task should be accepted cheerfully as a physician's duty, since the patient's memory for recent events often is poor, and sometimes that of the spouse is not much better. The patient should be examined every few days in order to chart progress. But more than that, the ability of the physician to demonstrate that a few fingers or toes can move a little will be very helpful to the morale of all concerned. Movement of a shoulder, thigh, elbow or knee may be equally encouraging to patient and relatives in the early stages. The physician is treating not just a lesion, not just a patient, but in effect a family situation, and it cannot be ignored. Proper splints or supports should be used as indicated. Passive and active exercises are to be encouraged.

Patients who have dysphasia need special help from nurses and relatives. In an ideal situation, a speech therapist would be present to assist in this respect. But ideal conditions for treatment are rare. Feelings of inadequacy on the part of relatives or friends should not preclude attempts to train the patient who has a speech disability. The patient may be allowed to sit in a chair or to attempt to walk in the first week or two, if the hemiparesis is mild. In the presence of complete hemiplegia, much retraining will be necessary.

SUMMARY AND CONCLUSIONS

An attempt has been made to point out the facts that not all acute cerebrovascular accidents prove to be vascular, and that not all of them are located in the cerebrum. A plea is made for clarity of thinking in regard to localizing the lesion and determining its nature. The first and important steps in this process consist of attention to detail in the taking of a history and in the making of a complete examination.

The need for general management of patients who have had a "stroke" is emphasized. Such patients need attention and a review of their progress at regular intervals. Improvement is directly related in part to the interest of physicians and relatives. These patients should not be left to work out all the details of care. The help of the department of physical medicine should be sought after the first week of the illness, provided the clinical condition of the patient permits it. Most hemiplegic patients can be trained to walk again.

Some Current Concepts of Viruses and Tumors*

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I AM VERY APPRECIATIVE of the honor of being asked to deliver the Christian Cancer Lecture. When I was invited, I did not attempt to conceal my limitations; I made it quite clear that I had done no laboratory work in this field for twelve years, being merely a spectator on the side lines. Previous to that, I had dabbled not a little in the fascinating subject of viruses in relation to tumors. But though I might even be classed as a tumor-virus addict, I wish to make it plain that I do not think there is any proof that viruses cause cancers in general, nor do I hold that as an article of faith. Viruses are the continuing cause of a few tumors such as the Rous sarcoma of fowls. Of most cancers we do not know what is the continuing cause. What I do believe is that viruses are as likely as anything else yet suggested to be the cause of cancer, possibly of most kinds of cancer; but we lack proof. Viruses have such properties as would make it quite possible for them to be the cause of cancer in general. I must, however, limit this statement still further: Viruses are not likely to be *the* cause of any ordinary cancer, for all cancers are probably brought about by a coincidence of several factors, maybe a virus and a carcinogenic chemical and yet other things. Even if the virus is the continuing cause which keeps the cancer going, some other thing, that which starts the malignant process off, may be what hits you in the eye.

I am particularly glad to be here, to attempt to answer a question. I had the pleasure of hearing Dr. Bittner lecture when he visited London last September. In his lecture he told us about a factor causing mammary cancer in inbred mice and transmitted in the mother's milk; you may possibly have heard of this! Towards the end of his talk, he pointed out that many of the properties of the agent, its size, chemical composition, stability to various agents, ability to multiply and so forth, all pointed to its being a virus. But, he asked, how can we consider it as a virus when it behaves so oddly, when its introduction does not lead forthwith to cancers, but these only develop later on in life when hormonal and other factors are just right for them? How can a cancer virus be transmitted for two generations without causing any cancers and only do so in a third generation?

Here is an apparent paradox which has troubled many people. It is my main task in this lecture to try to convince you that the difficulty arises only because most people have too narrow a view of how viruses ought to behave. The measles virus lays low almost every susceptible child with which it comes into contact. But not all viruses act thus. Let us forget about measles and look at some of them with different habits.

TYPES OF VIRUS ACTION

A virus may do one or other of several things to you. It may, as soon as introduced, invade your tissues and produce general or local disease. Then when your resistance is mobilized sufficiently to overcome it, it may be seen no more, its progeny having perhaps been passed on to another susceptible host. This is the "measles" type of behavior. The situation may be similar except that when the infection is over, the infecting virus may persist somewhere in the host; this happens with fowl pox and with psittacosis. Or again, the infection may be at no time clinically apparent: infection may occur unrecognized, but leave you with definite immunity (the most satisfactory state of affairs). Many children in the tropics thus acquire an immunity to yellow fever without any trouble or expense, and during a flu epidemic many people undergo a completely subclinical infection which nevertheless leaves behind it a useful immunity.

Most important are what may be called indigenous infections. These have three characteristics: (1) The infection is contracted at a very early age normally; (2) it is inapparent, and (3) at the same time it persists indefinitely. Its presence may be detected in one of two ways. Though not pathogenic to the host carrying the infection, the virus may be able to produce disease in other species or in other stocks of the same species, or indicator strains. There are many examples of this. In the United States almost all strains of potato carry a virus, harmless to them, but capable of inducing disease in tobacco and other plants. The virus of lymphocytic choriomeningitis of mice may produce no effects when inoculated into mice of a strain car-

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rying it, whereas mice of a virus-free strain may be fully susceptible (Traub[1]). So-called lysogenic bacteria may carry a bacterial virus producing no evident effects in them but able to lyse other organisms. Thus many strains of B. coli carry a phage, of which the presence is revealed when Shiga dysentery bacilli are used as test objects. The difference between the susceptible and resistant strains may be due to the fact that the latter are carrying the strain in a state of equilibrium with the tissues or are carrying some other virus which interferes with the first; or it may depend upon other causes perhaps genetic in origin.

The second way in which a latent virus may be detected is by activating it in the original host by application of some jolt or shock, which liberates it from restraint. Thus human beings carrying the virus of herpes simplex may come out in a crop of blisters on the lips when they have a cold or a fever or are exposed to ultraviolet irradiation. The same virus, herpes, may give rise to a chronic inapparent encephalitis in rabbits which flares up when the animals are given anaphylactic shock (Good and Campbell[2]). How these various stimuli work is still obscure. Lwoff[3] has investigated what happens in the case of a lysogenic strain of *B. megatherium*. Here every bacterium carries a symbiotic phage, dividing *pari passu* with the host cell, and not regularly liberated into the medium to be detected by use of an indicator organism. Lwoff calls this "pro-phage." Application of such a shock as ultraviolet irradiation causes a massive transformation of the symbiotic phage into the active lytic form, so that the whole culture lyses *en masse* is less than an hour after application of the shock. Obviously we have to consider whether carcinogens such as hydrocarbons may not come into the category of jolting stimuli which activate a latent infection with a tumor virus. With Ahlström, I was able to show that tar had the power of tilting the balance in favor of the virus in rabbits infected with Shope's fibroma (Ahlström and Andrewes[4]).

There live within our bodies hundreds of kinds of bacteria of which very few are normally pathogenic. Many of them grow on culture media, and even if they don't, we can stain them and see them. Is seems to me likely that there are also large numbers of undetected symbiotic viruses. Some we can detect because we have discovered "indicator hosts" or a suitable method of activating them, but these are perhaps in the nature of lucky flukes. There is no reason why suitable indicators should exist for our convenience in detecting every latent virus, nor why the host virus equilibrium should necessarily be always so unstable as to be upset by this or that stimulus. Many latent viruses may exist and await detection till we have perfected optical, immunological or other means of revealing them.

VIRUS MULTIPLICATION

The existence of innumerable latent virus infections admits, I think, of no dispute; nor does the fact of activation of many of these by the appropriate maneuver. Before we deal more specifically with tumor viruses, we need to consider other properties of viruses which have lately come to light. It appears probable that viruses do not multiply by binary fission of one infective particle giving rise to two infective particles. The matter is more complex. After a host—an embryonated egg, or a mouse—has been infected with influenza virus, the virus seems to disappear so that not even the particle originally introduced can be recovered. So, too, with many other viruses including the phages which attack bacteria. Here we have what is called an "eclim stage" during which no virus is demonstrable and which may occupy a considerable part of the developmental cycle of the phage. Much work is in progress to reveal what goes on during this cycle. It seems almost certain that the cycle is a complex one and includes a phase during which the virus exists in a form other than that of the virus we know and can demonstrate by electron microscopy. There is evidence that before a cell infected with influenza virus produces more complete infective particles, something appears having only some of the properties of the perfect virus; thus complement fixing antigen may appear along with hemagglutinin, ahead of the production of infectious virus.[5]

Studies of the virus of molluscum contagiosum of electron microscopy indicate that particles about 100 mμ across are formed before the typical brick-shaped elementary bodies 400 mμ in diameter can be found (Rake and Blank, 1950[6]). All this sort of thing has led me to wonder whether we are not looking at viruses rather wrong-headedly. We find a particle of fairly constant size and shape—brick-shaped for the pox viruses, having a head and tail for the larger phages. We note that it is very inert and lacks, as a rule, visible enzymatic activity and does not, as such, seem to be directly reproduced within the infected cell. It does not occur to us that the most important part of the virus' life is when it is in the obscure, undemonstrable but highly active stage of multiplication within the cell. Yet that, to my mind, is the real virus. The inert particle we know and can manipulate may correspond rather to the seed or the spore which is the means by which a plant gets about the world in its quest for a happy new environment in which to start raising a family. It may represent the reproductive as against the vegetative phase of the virus' life story (Andrewes[7]).

Such a notion will fit in very well with some of the things we know about latent virus infections. The most successful parasites do not kill their hosts: there is always a tendency towards an equilibrium in which parasite and host learn to tolerate each other. In the case of viruses this evolutionary tendency seems to lead to a progressively closer integration of virus and cell, so that the virus may be quite closely mixed up with the genetic apparatus of the host ("parasitism at the genetic level" according to

Luria[8]) and it may be quite difficult to disentangle parasite from host. Some things formerly thought to be part of the host seem to be turning out to be, after all, parasites. An example is furnished by the kappa particles of some races of the protozoon *Paramecium*.

Now while it is perfectly true that toleration between host and parasite and even their integration tends to promote survival of host, there is another side to the story. The parasite, if it is to survive as a species, must be able not only to survive but to get about to a fresh host. It may do this more readily if it learns the trick of what has been called "vertical" as opposed to the normal lateral or horizontal method of spread. In other words it acquires the knack of infecting its host's offspring instead of his neighbors. Instead of being infectious, it becomes inherited.

There are some viruses which can do this very well. Thus Lwoff's megotherium phage is carried to daughter and granddaughter cell without having to come out into the open at all and without, apparently, having much power to infect cells in any other way unless and until the application of a shock upsets the whole equilibrium.

It would seem that what is happening here is that the vegetative part of the cycle is quietly keeping the symbiotic virus ticking and that the virus could perfectly well dispense altogether with the reproductive part, involving genesis of lytic phage particles. Loss of this reproductive phase and obligatory dependence on the vegetative phase and hereditary transmission—here are ideas which may make viruses in relation to cancer not quite so fantastic.

Students of viruses are familiar with masked viruses—those which we know to exist but are not directly infectious for fresh hosts. Thus Shope's papilloma virus behaves like an ordinary infectious agent in its natural host, the cottontail rabbit. In the domestic rabbit, however, though it produces perfectly good warts, these are normally not transmissible to new rabbits: immunological techniques, however, reveal that the virus is still there (Shope[9]). Swine influenza virus, as Shope showed, may be carried in the pig lungworms in a masked phase to be demonstrated only by indirect means (Shope[10]). Human influenza virus, too, may apparently fail to develop to the fully infectious state, as when excessively high doses are introduced into allantoic sacs of eggs (von Magnus[11]) or when non-neurotropic strains are injected into mouse brains (Schlesinger[12]). All these examples would fall into line if we conceived that the vegetative part of the cycle was proceeding normally but that the reproductive part, the formation of more of the ordinary infective particles, was stultified. All gardeners are familiar with plants which grow and prosper but obstinately refuse to flower.

I mentioned earlier that one of the three characteristics of an indigenous virus infection was that it was contracted at a very early age. One can't start much earlier than the ovum or sperm. We have already had to consider vertical transmissions of a virus from parent to offspring—a process which may involve transmission in the germ plasm. We had better consider one or two instances in which this may be occurring. The virus of St. Louis encephalitis was first discovered because of the occurrence of cases in human beings bitten by infected mosquitoes. The deeper the investigators looked into the thing, the more it appeared that this happening was quite irrelevant as regards the normal natural history of the virus. This seems normally to be a parasite of domestic fowls and other birds. Though it may be carried by mosquitoes, the natural vector, according to Smith, Blattner and Heys,[13] is the bird mite, *Dermanyssus gallinae*. In this creature, the virus can apparently be passed in the ovum from one generation to the next.

The garden tigermoth, *Arctia caja*, can be bred in captivity with ease for two or three generations. But after that the caterpillars tend to die after becoming limp and flabby. It seems that the unfavorable environment of the breeding cage has a cumulative effect on several generations, gradually tipping the scales in favor of a latent virus. Much the same happens with many other *Lepidoptera* and the virus thus activated is commonly of the group causing polyhedral diseases. The infection when it turns up may affect tiny larvae only two or three days after hatching: this and other evidence suggests that infection is carried in or on the egg (Smith[14]).

A disease of sheep called Scrapie is common in Scotland and is manifested by incoordination and such itching that the sheep rub off their wool against fences. Its causation by a virus was long overlooked since it was not expected that the incubation period might be as long as two years, as seems to be the case. Scottish farmers know of "scrapie rams" which beget lambs destined to develop scrapie when they're about two years old. The ewe which bears them may show no signs of being infected (Greig[15]).

Fowl paralysis, a disease on the borderline between ordinary infections and tumors, seems to be transmissible in the egg or from an infected cock. Alternatively chicks of a susceptible strain may pick it up after hatching but only within a few weeks of that time.

A stock of mice studied by Traub[1] was infected with lymphocytic choriomeningitis. During the two years or so he had it under observation, the state of affairs became altered so that ultimately all mice were latently infected *in utero* and no disease was apparent in the colony at all.

The virus' power of infecting fresh hosts in the ordinary way may not be lost altogether, but it may operate only where very young animals are concerned. One of the neurotropic mouse viruses will infect, by inoculation, any mouse; but natural infection *per os* is effective only for baby mice a few

(Continued on page 112)

The Wendell Hughes Method of Plepharopoiesis

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NO originality is claimed for the procedures used in the construction of new lids as outlined briefly in this paper. These two illustrative cases are presented chiefly because of the ease with which the operation can be done and because of the uniformly good results obtained. The procedures are fully outlined in a monograph entitled "Reconstructive Surgery of the Lids," by Wendell L. Hughes and published by C. V. Mosby in 1943. Dr. Hughes not only gives the historical development of the use of different materials in lid reconstruction but presents the material refined in the light of his own extensive experience in plastic surgery.

Essentially the method consists of making a new lid in two separate layers. The inner layer comes from the existing good lid, or donor lid. The outer layer of the new lid is usually a sliding or Celsus skin flap from areas immediately adjoining the resected lid, or it can be a free skin flap. To obtain the inner layer for the new lid the existing, or donor lid, is split transversely into two layers (fig. 1). The outer layer consists essentially of skin and orbicularis muscle. This part of the donor lid is not further disturbed. The posterior layer is essentially tarsus and conjunctiva. This posterior layer is used totally, or in part, by drawing it across the globe and suturing its free margin to the free margin of conjunctiva in the opposite cul-de-sac. This method of utilizing the posterior, or conjunctival-tarsus layer in blepharopoiesis is original with Hughes, although two other slightly similar methods occurring in older literature are quoted by Hughes, namely that of Köllner and that of Dupuy Dutemps.

This posterior layer provides a well vascularized healthy layer of conjunctiva which is absolutely essential to the continued health of the eye and at the same time furnishes a layer of tarsus so necessary to maintain normal thickness and lend form to the new lid. Lastly, a Celsus, or sliding skin flap is moved in to furnish the cutaneous layer of the new lid. The Celsus flap margins are sutured to the remaining skin margins of the damaged lid and also to the anterior, or undisturbed layer of the donor, or undamaged lid. This produces, from above downwards, one continuous sheet of mucosa-tarsus, muscle and skin covering the eye and does not immediately produce two *separate lids*. In other words, the new lid is splinted with, or to, the old lid margin (fig. 2). The Celsus flap thus has

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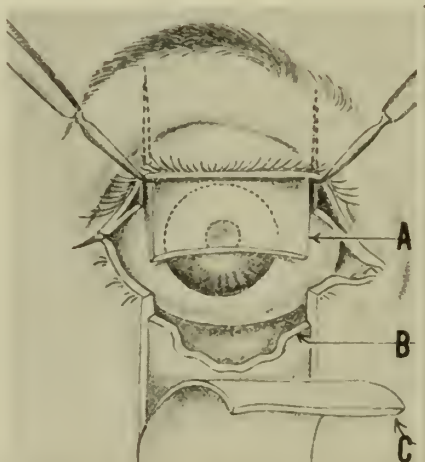

Fig. 1. Identification: *A.* Tarsal-conjunctival tongue or sliding graft. *B.* Free edge of conjunctiva in cul-de-sac. *C.* Sliding cutaneous graft. The defect in the lower lid remains after injury or following surgery of malignancy. Upper lid has been split or separated into an anterior and a posterior layer. The posterior layer has been incised vertically in two places and the central portion or tongue loosened to allow it to be drawn down into the defect where it is sutured to the free conjunctival margin. A sliding full thickness skin flap is loosened below and will be brought up and sutured to the freshened free margin of the anterior layer of the opposite lid.

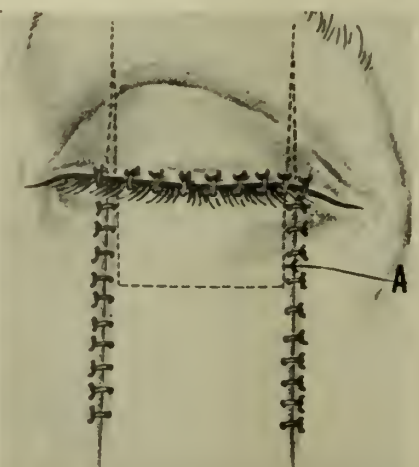

Fig. 2. Identification: *A.* Tarsal conjunctival tongue or sliding graft from upper lid. Completed first stage of blepharopoiesis. The celsus skin flap is sutured to the freshened free edge of the upper lid; its vertical edges to the adjoining skin margins. The sliding conjunctival-tarsal flap has been sutured to the conjunctiva of the lower cul-de-sac below and laterally. (Stitches are not shown on the mucous membrane.)

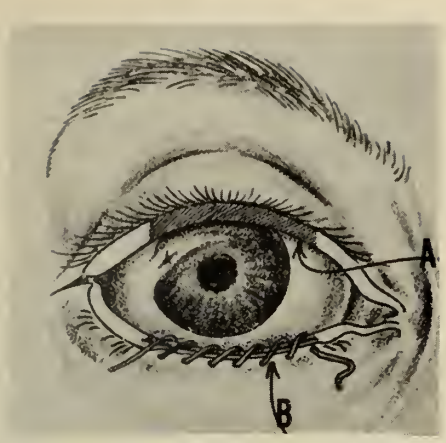

Fig. 3. Identification: *A*. Area of lid margin left bare after separation of lids. *B*. Running suture through conjunctiva and skin. After two to six weeks the two lids have been separated. A running suture needs to be placed in the upper lid in the same manner illustrated in the lower lid. If cilia are desired they must be transplanted at least three weeks before the above separation of the lid margins takes place.

a better chance of survival by receiving nutrition or blood supply from four possible sources: the skin margins of the damaged lid, the underlying bed of tarsus and conjunctiva, the free margin of the donor lid, as well as the slight blood supply inherent in the flap itself.

In the absence of suitable material in the better lid, as from careless roentgen therapy, a variation may be used. Instead of drawing a conjunctival-tarsus layer from, and still attached to, the opposite lid, a free conjunctival-tarsus graft from the upper lid of the opposite eye may be used. A Celsus flap of skin and orbicularis muscle is now used to cover this free graft. As another variation, one may use an attached conjunctival-tarsus graft and overlay this with a free skin graft from the upper lid. The free graft can be taken so that part of the brow will furnish the cilia for the new lid. As with all free grafts these variations are more pregnant with the possibility of "non-take" than in the method first mentioned.

As in any skin graft procedure, adequate hemostasis and removal of clots is necessary to insure viability of the grafts. Needless to say, an adequate postoperative pressure dressing that effectively bridges the gap between too much and too little pressure is a requisite for a successful take. Too much pressure produces an ischemic necrosis; too little pressure does the same by allowing clots and serum to collect between layers. Slow absorption of the clots and

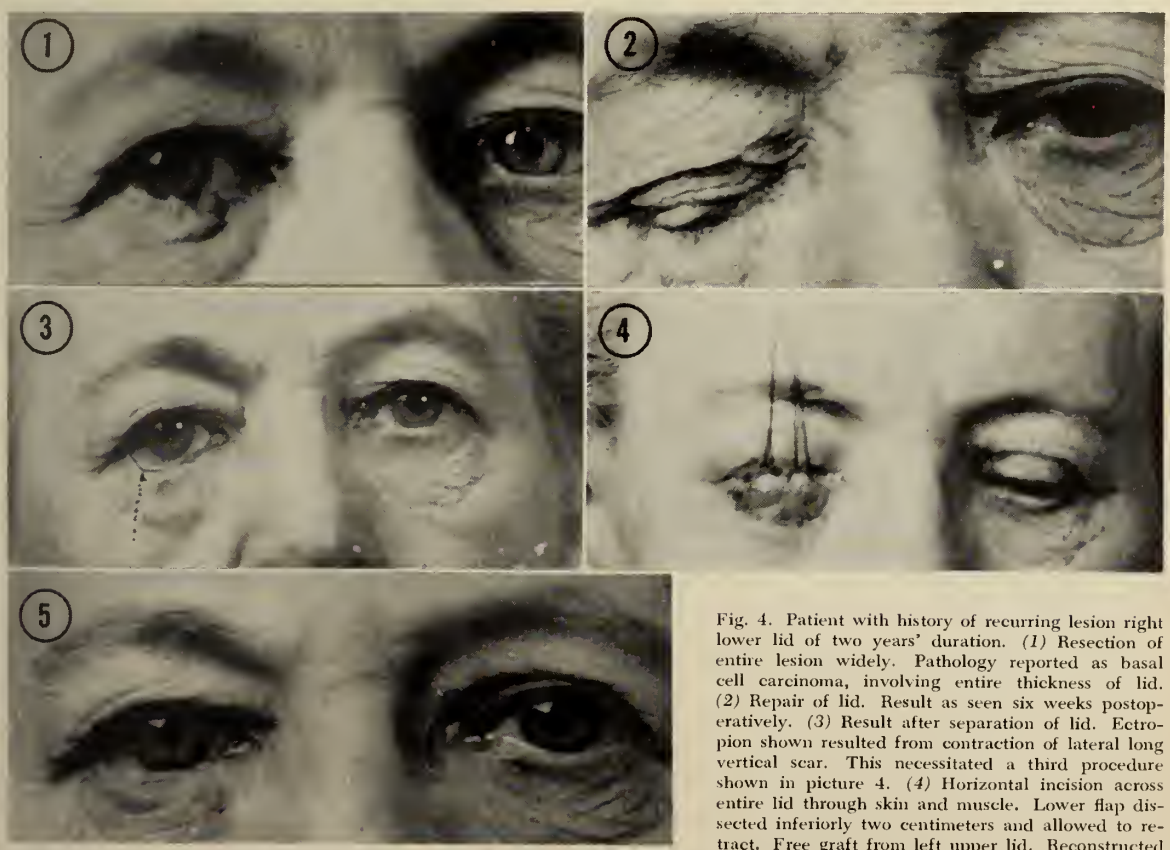

Fig. 4. Patient with history of recurring lesion right lower lid of two years' duration. *(1)* Resection of entire lesion widely. Pathology reported as basal cell carcinoma, involving entire thickness of lid. *(2)* Repair of lid. Result as seen six weeks postoperatively. *(3)* Result after separation of lid. Ectropion shown resulted from contraction of lateral long vertical scar. This necessitated a third procedure shown in picture 4. *(4)* Horizontal incision across entire lid through skin and muscle. Lower flap dissected inferiorly two centimeters and allowed to retract. Free graft from left upper lid. Reconstructed lid held in over-corrected position by stay sutures attached to forehead with tape. Lower lid was in over-corrected position before free graft was applied. *(5)* Final result of reconstruction right lower lid. Cilia not well seen but are all present.

serum seriously interferes with possible viability of the skin flap or free graft.

Some of us have seen reconstructed lids that resembled retracted flippers much more than normal flexible eyelids. This cosmetically objectionable result is largely eliminated by the splinting procedure inherent in the method just described. Retraction from scar tissue formation is thereby largely eliminated. This important point of attaching or splinting the new lid to the opposite lid in any major or minor plastic procedure on the lids cannot be too strongly stressed.

Dr. Hughes uses a very workable method of transplanting hair to furnish a new supply of cilia for the reconstructed lid. While some of my results of hair transplant have been somewhat sketchy, none of the transplants have failed to take. Malle in France as early as 1891 criticized the cosmetic deformity in a lid caused by lack of cilia. Various transplant methods of doubtful value were used until Paul Knapp in 1908 reported the first free graft of skin from the eyebrow into the margin of a new upper lid he had constructed. He was unable to follow the case for more than a few weeks and reported the method a failure because the hair in the transplanted graft had fallen out by that time. Nine years later he saw the patient again and he appeared with a complete row of eyelashes. The cilia had grown in again after the patient had left Dr. Knapp's care. This case was reported again in 1917, and independent results by the same technique reported by John Wheeler in 1920 and 1923.

This hair transplant is done two to eight weeks after the first mentioned reconstructive procedure has been carried out while the lids are still attached together. It is determined where the line of separation will be when the lids are eventually separated. A groove is incised in the skin parallel to but two to three mm. above or below this line, and extending to the tarsus. A full thickness strip of skin at least four hair follicles in width is removed from the nasal end of the lower edge of the eyebrow, fitted into the prepared groove, and sutured in place with 6-0 silk. The ipsilateral brow is used for upper lid lashes and contralateral brow turned end for end is used for lower lid lashes. This choice of tissue source cares for the correct angle of subsequent growth of cilia in the finished lid. During healing all transplanted hair falls out. Only the central one or two rows of hair grow in again later on. The outer rows of follicles have been so damaged by surgery that viability is not possible. This hair-bearing free graft from the brow is much thicker skin than that composing the new lid but it must again be emphasized that the thickness of the graft must not be trimmed away or the hair follicles will be trimmed away too and no hair will grow from this transplanted skin. Appropriate pressure dressings will help the graft to take. Collodion dressing to the transplanted hair directs the angle of growth of subsequent cilia. After three to six weeks the lids are separated with scissors and the skin layer and conjunctival layer of each margin is sutured with a running suture and a light dressing applied.

In the reconstruction of the upper lid any resulting impaired levator action must be dealt with later. In one of the cases presented, fully two-thirds of the levator must have been removed with the original lid tumor but no apparent elevation defect has resulted.

While the above description merely touches the more important points of the procedure the actual operation is no more difficult than here described. The cosmetic results are so excellent and can be obtained so easily even by those who operate just occasionally that this method of lid reconstruction is recommended unhesitatingly to any ophthalmic surgeon.

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The Blood Pressure Problem*

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One problem given to me as a young physician starting practice in Philadelphia, was to take over the responsibilities of the office of an outstanding doctor. In the summer he would travel to Europe, partly for a vacation and partly to see some of his well-appointed patients. The second summer after the chief had departed an executive from a Philadelphia store came to the office complaining of some pain in the wrist and arm. A careful, complete check and re-check was made of this man. To my consternation the blood pressure ranged from 220 to 240 systolic and 110 to 125 diastolic. In a conscientious endeavor to protect the patient, much ado was made of the hypertension and relatively little attention was paid to the pain in the wrist. The patient was seen twice weekly for six weeks and by the time the chief returned the doctor was unhappy and the patient depressed. On making my report to my superior I called his attention to the fact that I had found a marked hypertension in this man. After sizing up the situation and seeing what a botch I had made in the management of this patient the chief gave me a lesson which I shall never forget. He said: "Doctor, this man has had high blood pressure for twenty-five years. I have known it and, from time to time, mentioned it to the patient. However, he was never disturbed. In no way did his pressure limit his work. He was a man of moderate temperament and mild tastes and, therefore, was easy to control. With attention to diet and small amounts of sedatives no damage occurred. Yet, in your zeal to protect him because of the blood pressure he becomes demoralized and altogether he has had a most unhappy summer."

Another example comes to mind. In 1905 Dr. W. S. Thayer of Johns Hopkins tried out the newly invented blood pressure apparatus on a friend and patient who had consulted him for a minor complaint. When the blood pressure registered 200 mm. Hg. Dr. Thayer was disturbed. The available knowledge, at that time, suggested that one could not live long with such an elevation in blood pressure. The good doctor observed the man for a long time and was embarrassed to note his continued well-being. Finally, the patient outlived Dr. Thayer. About the time of Thayer's passing his patient had decided to marry again and start raising a new family.

It should be kept in mind that blood pressure is a symptom and not a disease. As a matter of fact, we can classify blood pressure for practical purposes as normal with a systolic perhaps between 100, 130 or 140 and a diastolic of 90 to 100; low blood pressure below 100 systolic and high blood pressure over 150 systolic. We cannot take the insurance companies' statistics too seriously. It is difficult to establish an accurate range of the blood pressure in any individual without having made a good many separate observations and studying the patient under varying conditions of activity and rest. The fluctuation of the blood pressure as long as it is fairly stable at any particular level is much less dangerous than the rapid fluctuating type of blood pressure which is noted in emotionally hyperactive individuals.

I like to explain blood pressure problems to my patients as one explains the pressure of an innertube in an old automobile tire. The higher the pressure and the weaker the wall the more likely is a "blow out" to occur, which may be brought about by given circumstances. Old blood vessels and old innertubes can be safely used over a long period of time if the urgency and tension of everyday life is moderated. Blood pressure need not shorten a person's life. However, the higher the blood pressure and the more strenuous the life of the individual, the less likely is he to enjoy the benefits of old age. Insurance statistics indicate that high blood pressure may have an adverse effect on the length of life. However, if the heart compensates and becomes moderately enlarged it may carry the increase in blood pressure over an extended period of time. In many cases blood pressure

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does not shorten life. Dr. Louis Dublin, in his fascinating study of "The Facts of Life" has pointed out that death rates from heart disease and hemorrhage of the brain are high in people with elevated blood pressure. Also, the death rate from kidney trouble is high because the kidney is ofttimes implicated in high blood pressure. Yet, Dublin is careful to point out that elevated blood pressure may not be inconsistent with a long, happy life, and a generous measure of useful activity. When the individual follows the rules laid down by his doctor, he often is capable of carrying on and leading a virtually normal life.

Women are likely to carry high blood pressure more satisfactorily than men. I believe this is due basically to the difference between the structure of the coronary vessels and the other vessels of the body in the female and male. Dr. William Dock has shown in an excellent pathological study that the coronary vessels in the male in certain of their branches have a much thicker wall than in females and, therefore, are more likely to go into spasm and be the site of occlusion.

Due to the particular strains and activities which doctors carry on they are, according to statistics, twenty per cent more likely to develop diseases of the blood vessels and particularly hypertension than other white males of the same age. According to most recent and reliable statistics for diseases of coronary arteries physicians show an increase of eighty per cent over white males of the same age. This may be due to earlier diagnosis since physicians should be more readily investigated. (This point must be offered with some reservation.)

I have known a good many physicians with high blood pressure. Two distinguished American physicians, after being under expert treatment for a number of years, finally decided to forget about the blood pressure and not have it taken. Each one went on an extended three months' vacation and after having been separated from their strenuous activities for this period they had a drop in blood pressure of more than fifty per cent. Since that time one of the doctors has died from an abdominal organic condition not related to blood pressure while the other man's blood pressure continues slightly above normal. He is enjoying himself and has dismissed any concern of his blood pressure.

In an excellent study in diseases of old age, Robert Monroe, from Boston, points out that in studying more than 7,900 cases over 61 years of age, the data on increase in blood pressure was of considerable variance from that given by insurance statistics. He found that a great majority of men and women over 61 have an elevation in blood pressure. He mentions that in the majority blood pressure increases with age except in a very few old men where there was a mild recession to less than fifty per cent. Indeed, Monroe believes that it is unusual to find an old man or woman who shows values of blood pressure consistently below 140-90. General practitioners who have had much experience in studying the variations of blood pressure in older individuals agree that most older people have high blood pressure. Therefore, the attitude, interpretations, and statistics of the insurance companies should be re-examined and re-interpreted.

I would venture to advance the statement that in more than fifty per cent of cases of persons with high blood pressure, the less said about the blood pressure the better for the patient and the doctor. In seventy-five per cent of the cases it does not matter. In the other twenty-five per cent it might matter a great deal. Overall interpretation of the background of the individual, how long he has had the blood pressure, his emotional makeup, the stress and strain under which he lives, his hopes, fears, and aspirations — all these have an intimate relationship to the blood pressure. Monroe points out that the serious disorders in which high blood pressure plays an important role are found almost exclusively in individuals in early adult, or middle age, or in other words in those interested in the purchase of life insurance. In studying records of 8,000 people over 61, Monroe failed to find one case of malignant hypertension.

Blood pressure does not necessarily increase with age but it does vary upward or downward according to other influences and emotional stresses. This fact is more important than the age of the individual, in understanding the possible relationship between blood pressure and occlusion of blood vessels in the brain, heart, kidneys, or extremities. Many individuals with thrombosis of a cerebral or a cardiac artery have normal or only slight increases in the blood pressure. In these individuals it is the defect in the walls of the blood vessels which is important rather than the pressure within the arteries. Granted cerebral hemorrhage usually results from increase in the blood pressure yet in many cases, as Monroe points out, the blood pressure was often normal shortly before the stroke and the pressure after the stroke, if life persists, might become high for the first time, or remain un-

changed, or return to normal. More patients with non-valvular heart disease have hypertension than those with coronary artery occlusion. And, many individuals with normal blood pressure suffer from diseases of the coronary arteries. Accordingly, one should not be too hasty in placing an obligatory relationship between high blood pressure and occlusion of arteries. In the early stages of high blood pressure the emotional reaction of the individual to physical shock, continual physical stimulation due to sustained drive, worry, sexual overstimulation, and similar tensive experiences is important. A marked increase in the systolic pressure may take place but the diastolic pressure ofttimes remains fairly stable at 90 or less than 100 mm. Hg.

TESTS TO DETERMINE LABILITY OF PRESSURE

Sedation

Sodium Amytal Test. Undue elevation of pressure due to stress, notably at the time of examination, evokes the thought, "I wish I could take the pressure with this patient asleep." There are two methods for doing this. The patient may be put completely to sleep with intravenous sodium Pentothal, followed by coramine to waken him, or the sodium Amytal method may be used. The latter is much to be preferred. In either case a preliminary series of pressure readings is taken at complete rest until a satisfactory base level is obtained.

Sodium Amytal is given 0.2 gm. (3 grains) every hour for three doses. Blood pressure determinations are obtained at base level with the first dose, then each half hour until two hours after the last dose. With moderate to severe elevations of pressure a drop of 40, 50 or more mm. Hg systolic and 30 or more diastolic is satisfactory.

Sodium Nitrite Test. After base readings are obtained 65 gr. (1 grain) of sodium nitrite is given every half hour for five doses. Blood pressure readings are taken every half to two and one-half hours after the last dose of nitrite. Lowering of pressure similar to that of the sodium Amytal test is acceptable, and the duration of the depressor effect after the final dose is also significant—favorable if returning to base levels only after two or more hours, less so if returning at one-half or one hour.

Cold Pressor Test

The purpose of the test is to determine the degree of hyper-reactivity of essential hypertensives and of normals. In the case of the latter, hyper-reactors are presumably potential hypertensives. Basal blood pressure is obtained. The left hand and wrist are immersed in ice water for one minute. Readings are taken at one half and one minute, then every one or two minutes until pressures reach initial level. There has been no universal agreement as to what constitutes normal and excessive responses. A rise of 30 mm. Hg systolic and 20 mm. diastolic is an acceptable dividing line, as in persons with normal blood pressures 85 per cent react normally, and the 15 per cent of hyper-reactors are candidates for future hypertension, whereas among the established hypertensives, those with excessive responses appear to have a less favorable outlook than those with less marked or normal responses. Pressure should return to base level within four minutes.

LOW CHOLESTEROL-LOW FAT DIETS IN PREVENTION AND TREATMENT OF ATHEROSCLEROSIS

Low cholesterol and low cholesterol-fat diets tend to prevent and aid in treatment of atherosclerosis, especially of the coronary vessels. The rice diet is used at times because it is low in fat, protein, and cholesterol.

The experimental results supporting the concept that deposition of lipid, especially cholesterol and its esters, is the prime pathogenic mechanism of atherosclerosis. That lipid is deposited in quantity all will agree. Can it be prevented by diet?

1. Atherosclerosis appears most commonly and severely in those people who take diets rich in fat and cholesterol, and who in addition are well fed. The disease appears in many people who have not consumed fat diets. Therefore, diets low in fat and cholesterol do not guarantee freedom from atherosclerosis.

2. All physicians of experience can testify to the importance of heredity. Even with bad heredity, it may be possible to alter, or even prevent, an inexorable pattern unyielding to environment from expressing itself daily. It is not known whether families in which atheroscelrosis is dominant would be benefited by diet.

3. The Eskimos take large amounts of lipid without any clear evidence that they suffer from unusual degrees of atherosclerosis. Those people who eat little fat are said to be unusually free from the disease. Evidence from starvation areas suggests, but far from proves, that atherosclerosis is less common among the badly nourished than the better.

4. At high levels there is a close relationship between serum cholesterol levels and the occurrence of atherosclerosis. That is levels above 400 mg. per 100 cc. serum, when maintained for long periods of time, lead to increase in incidence and severity of atherosclerosis. With more normal levels the problem becomes much less clear. Some believe that small increases above the accepted normal lead to, or at least accompany, coronary artery disease.

5. Does undernourishment prevent coronary disease? Observations made on Okinawans, Costa Ricans, and prisoner of war camps suggest, but do not prove, that gross malnutrition is unassociated with coronary sclerosis.

Certain nomads living on a high animal fat diet exhibited a high incidence while their contemporaries living in the towns on a mixed diet did not. More information is required before observations such as these are acceptable.

6. Do some people, like herbivorous animals, develop lipemia and possibly atheroselerosis while others, more like omnivorous animals, do not. Studies have proven that this is true. There is an extraordinarily wide variation in the lipemia developed in some people on a high fat-high cholesterol diet as compared with others. Whether these are the people who will develop atheroselerosis remains to be seen.

7. Is there a direct relationship between the lipid content of the diet and the level of blood lipids. The evidence is conflicting. Opposed are the findings (1) that the blood lipids are no higher after a high milk, cream, and egg diet used for treatment of ulcers than before; (2) that no relationship was found between the lipid intake and blood level in families with essential familial hypercholesteremia; and (3) none in nephrosis when the diet was varied widely. Favoring are the observations (1) that in some people at least, blood lipid levels rise with large amounts of dietary lipid; (2) the lipid level is somewhat higher in well-fed populations, especially when dietary lipid is high; and (3) the incidence of atherosclerosis seems to be greater in those countries in which the use of dairy products is high.

8. Is a low cholesterol-low fat diet practical? Yes. But within severe limits. For the people in this country it would currently be wholly impractical. It can be used in certain families when the wife is interested in preparing the diet. Like any severely restricted diet, it constitutes a large psychological handicap.

9. Do low fat-low cholesterol diets satisfy the requirements of an adequate diet? Most do not but can be made to do so. The ordinary lipid-poor diet causes constipation or diarrhea, much gas and poorly formed stools. The patient does not feel well on the diet.

10. Weight loss does usually occur and may be severe. This is not necessary but it is usual, especially in those who have been accustomed to large lipid intake. Cholesterol levels are not elevated as a result of weight loss. But in general these diets should be as nearly iso-caloric as possible in order to avoid weight loss and starvation lipemia.

11. What foods are lost in the diet? Eggs, milk (except skimmed), cheese, butter, and oleomargarine, fatty meats, shellfish, and pastries rich in eggs and milk. This constitutes a very imposing loss. To be sure this is so, try it and find out the results.

12. Does rigorous exclusion of lipid from the diet lower blood cholesterol? Yes, but the diet must supply less than 100 mg. of cholesterol a day. The exclusion of fat, animal or vegetable, is quite as important.

13. Does alcohol provide a good caloric substitute in a lipid poor diet? From many points of view, yes. This and the unpalatability of the diets are probably as good a reason as any for drinking. This is no substantial evidence that alcohol aids in atherogenesis or that it dissolves the lesions once they are present, except in concentrations used in histological preparations.

THE MANAGEMENT OF HIGH BLOOD PRESSURE IN INDIVIDUALS OVER FIFTY

The first essential in the treatment of high blood pressure in persons over 50 is a clear understanding of the patient. Certain major facts such as the weight, the presence or absence of lesions in the brain, heart, kidneys, or vessels, the type of work, diet, rest, elimination, periods of recreation, all play a part in the management of the patient with high blood pressure. Not rarely do patients with a considerable elevation in the blood pressure, perhaps around 180 or 200 systolic, experience a considerable let-down when the blood pressure has been reduced, if it can be reduced to 140 to 150. Let me add this thought—sensitive individuals when the blood pressure is taken for the first time may show a marked elevation. Consequent readings may reflect a normal pressure. The fluctuation is important.

Before passing on to the consideration of drug therapy let me say a word about the surgical treatment. A review of the work of Adson, Craig, Smithwick, and Max Peet, and others, indicate that a certain percentage of individuals, not over one out of three, show permanent reduction in the blood pressure. In a personal communication with Craig, of the Mayo Clinic, after he had reviewed 500 cases of sympathectomy for hypertension, he told me that the important results experienced by the patients—forty of whom were doctors—was the relief of headaches which occurred before the operation, and the elimination of the anxiety drive from the hypertension which they experienced preoperatively. However, a considerable number noted an annoying pressure and distention of the abdomen and some girdle pains. I have recommended, in the past, a number of patients for sympathectomy. As time goes on, there is a somewhat more reserved attitude. One knows waves of enthusiasm for various technical procedures. For example: total thyroid removal for congestive heart failure, which is now in the discard; vagotomy for peptic ulcer is now, so far as I can determine, on the wane and perhaps sympathectomy for high blood pressure will become regarded as an operation of value for a small percentage of patients.

In patients with involvement of the parenchyma of the kidneys reduction of the blood pressure may be fraught with danger. Before a marked reduction is planned, a complete knowledge of the vascular system should be obtained. The emotional side of the patient should be considered, that is, his attitude not only towards his blood pressure but his business, his family, his associates, and his general outlook on life. One should always keep in mind that many individuals are carrying a marked increase in the blood pressure without any symptoms. Striving to reduce a mild increase in pressure may thoroughly upset a patient. Nowhere is the art of medicine

more important than in the management of the patient over 50 with high blood pressure. These patients show weakness, abdominal cramps, lethargy, oliguria, azotemia, and disturbances in acid base balance.

Today the opinion is that since there are hazards connected with the low sodium diet, the rice diet, and with semi-starvation, it can be properly assumed that the best diet for the patient with hypertension is one that throws the smallest burden on the metabolism and yet preserves strength and vigor for the longest period. So often the patient on a rigid regimen may find after the diet is abandoned that he is in a worse state than before the treatment was begun. I also supplement the diet in older individuals with a whole vitamin B complex in the form of brewer's yeast tablets from 15 to 25 daily.

The excessive use of coffee, tea, and alcohol in susceptible individuals will bring about an increase in the blood pressure by influencing the nervous system and the vascular system. Granted that many persons may use strong caffeine drinks, tobacco, and alcohol with no interference, the fact remains that many are susceptible to these agents. The earlier the person eliminates the substances which are unfavorable for him and stays away from them, the less trouble he will have from the use of them.

THE RICE DIET

1. Allow 200 to 300 gm. dry rice daily. Boil or steam rice without the addition of salt, milk, or fat. The rice will provide 700 to 1,050 calories.
2. Allow fresh or canned fruits. If substances other than sugar are used for the preservation of fruits, such fruits must not be used. Dates, avocados, and dried fruits are avoided.
3. Allow brown or white sugar, honey, molasses, or Karo syrup.
4. Allow about 1,000 cc. of fruit juices but no additional water.
5. Prescribe supplements of iron and vitamins.
6. Continue this diet for six weeks or longer.
7. This diet provides for each 2,000 calories, about 20 gm. protein, 5 gm. fat, 460 gm. carbohydrate, and 0.2 gm. sodium.

The efficacy of the rice diet may be its low sodium content which is easy to achieve, its low protein level, low calorie level, or some other factor.

McLester states: "The rice cure advocated by Kempner warrants the same generalizations as those given for sodium restriction. Such drops in blood pressure as occur during this regimen are generally credited to the low sodium intake rather than to the extremely low protein quota of the diet. Schwartz and Merls say that it results in negative nitrogen balance. Opinions differ, and the good results reported by Kempner await further confirmation.

There is danger of depletion of body sodium especially if the kidneys are damaged. It has been pointed out that poor results may be expected with the rice diet, for example, if the urine specific gravity remains fixed at 1.010.

DIET AND HIGH BLOOD PRESSURE

The quality and quantity of food one eats may have an important influence on the blood pressure. Continual overeating in persons predisposed to increase in blood pressure certainly dooms that person to persistent high blood pressure. On the other hand, the quality of food when restricted to moderate quantities may exert a preliminary influence in reducing blood pressure to normal. The successful business man whose success in a certain sense may be judged by the extension of his belt line and the kind of clothes he wears would be wise to avoid the increase in his girdle line if he wants to protect his life-line.

The special diets with use of rice, other vegetarian diets, and other unpalatable diets are not usually satisfactory. It has been known for a long time certain minerals, notably the sodium ion of sodium chloride, exert an influence on the osmotic pressure of tissue fluids and with the retention of water in the body produces an increase in the blood pressure if its use is continued long. On the other hand, a well-balanced diet such as the following has proven very helpful.

There are two points on which most authorities agree:

1. The importance of a "calm and philosophic outlook on life" cannot be over-emphasized.
2. Loss of excessive weight almost invariably leads to some improvement and should be imposed as a first dietary modification when the patient is obese.

THE MEDICAL PROBLEM FOR THE CONTROL OF HIGH BLOOD PRESSURE

In a recent edition of the British Medical Journal for March 15, 1952, emphasis was laid on the fact that today the most important disorders were essential hypertension, atherosclerosis, rheumatic fever, and cancer. Of these four mortal diseases, high blood pressure is the most common, according to this editorial. It is present in five per cent of young adults, thirty to forty per cent of adults over 40, and approximately seventy-five per cent of all persons over 70. It is slightly higher for women. High blood pressure causes from some fifteen per cent to twenty per cent of deaths in people over 50.

Sixty per cent of these are cardiac, twenty per cent cerebral, and ten per cent renal.

What happens over a period of years in untreated individuals? Certain important data are available—first, the death rate in men is about one and one half times that in women except in the cases of malignant hypertension, when it is approximately the same. Second, the prognosis in any group varies greatly on the quality of the patients and the survival rates can be compared only when the patients are grouped according to certain well defined criteria.

Four grades of severity of high blood pressure are accepted today. However, in this grouping in the light of modern knowledge not enough attention has been paid to occlusive coronary atherosclerosis as a complicating factor which may alter the entire course of the disease. The death rate for cases of essential hypertension is about double that of the general population.

It has been shown that the surgical treatment in a certain percentage of cases has lowered the fatality rate of high blood pressure. At the present time, a number of comparative observations on series of patients treated surgically and series treated with new drugs is being carried on, as yet no conclusions have been reached. However, conservative treatment in the past has meant little beyond increased rest and relaxation with weight reduction and the avoidance of nervous and physical stress plus the use of sedatives. With this treatment about sixty to seventy per cent of patients with mild to moderately severe high blood pressure may remain more or less free of symptoms. Headaches, sleeplessness, vertigo, and fatigue noted in patients with high blood pressure are frequently due to an anxiety neurosis. Here psychiatric help and the moral support of a good understanding doctor may bring the blood pressure down to normal. Much of the earlier criticism of the surgical technic was based on the belief that the drama associated with the operation might well cause the relief of symptoms.

It has been reported that seventy per cent of patients using the rice diet show objective improvement. Even changes in the "T wave" of the electrocardiographic tracing may be altered for better. The basic feature of the rice diet is its low sodium content which in no event must exceed 0.5 g. each day.

The use of cation-exchange resins for the control of sodium transport in the body is being used more and more in the control of blood pressure through diet.

Hexamethonium bromide has been used with considerable success in the maintenance of blood pressure control. It may be given by oral or parenteral route. Hexamethonium tartrate has been used when large doses are necessary to avoid the risk of bromide intoxication. It has been noted that hexamethonium tartrate should be combined with a low sodium diet.

As a rule the oral administration of hexamethonium (between 250 and 750 mg. three times daily) may alter the blood pressure. It may be necessary to change the diet to avoid the altering of the doses of hexamethonium. The body may develop a tolerance and this can be identified within the first three months. After that even smaller doses may be used. Side effects from the use of hexamethonium have been less troublesome although they have been noted.

Other drugs for the reduction of high blood pressure such as thiocyanate, and Veriloid often cause vomiting as have also various adrenergic blocking agents such as dibenamine.

Relatively benign hypertension does not need any of these drastic methods. The only groups in which surgery should be considered is in group four, where there is pronounced and persistent malignant tension. The most promising drug today is hexamethonium.

THE PREVENTION OF HIGH BLOOD PRESSURE

In Plato's philosophy of old age he makes the comment: "He who is a calm and happy nature will hardly feel the pressure of age." One might add, "will hardly feel the high blood pressure of age."

Increase in blood pressure has taken on unusual importance because of its popularity with insurance companies in their appraisal of prospective risks. A good many applicants have been turned down by these companies because of a mild increase in their blood pressure and it has frequently turned out that the applicants have lived longer than the doctors who have examined them.

Hypertension may be classified as one of the penalties of the high pressure of modern daily existence. It is a frequent finding in the overzealous, energetic individual who is ambitious to gain position, fame, and wealth. Highly competitive life with its sharp contrasts and defeats when acting upon sensitive individuals is likely to produce a state of continual mild excitement. Over-stimulation of the adrenal glands and the secretion of hormones from the pituitary, thyroid, and adrenal glands may bring about a continual peripheral vasoconstriction. Which of these hormones causes the effect is not important. What is important is that the tension and

(Continued on page 117)

A Visit to a Japanese University Hospital

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While stationed at Itazuke, Kyushu, on the southernmost island of Japan, some of us with the 58th Medical Group, 58th Fighter Bomber Wing were fortunately able to visit the Kyushu University medical school and hospital in nearby Fukuoka. This institution stands among the leading centers of medical education in the Far East.

Accompanied by an interpreter, we visited the surgical department where we met Dr. Tomada, professor of surgery, who like all Japanese people was quite solicitous in his attitude toward us. He was pleased to know that I had trained under Dr. Owen H. Wangensteen and was happy to learn something of Dr. Wangensteen's recent surgical interests and papers.

A total gastrectomy for a cancer of the stomach was scheduled for the morning. Perusal of the patient's chart revealed an excellent preoperative workup with extensive laboratory data. Medical education in Japan has been impeded because of a language difficulty. Before World War II, the German language was employed extensively—all books were imported from Germany and much of the medical literature reported by Japanese medical scientists was written in German with only a smattering of Japanese. In 1946 English unofficially became the preferred medical language. Hence it was imperative that all medical students and doctors acquire a reading knowledge of it. However, German hasn't completely disappeared from the medical vocabulary and consequently, one sees a combination of English, German and Japanese being used. All three languages were recorded in the patient's chart in one section or another. The medical history and physical examination were described in German or Japanese and the laboratory data in English or German. Despite a reading knowledge of English, very few are capable of speaking our language.

The scrub suit was dark blue, worn over the street clothing; wooden clogs on bare feet (typical indigenous Japanese footwear) were used in the operating room. After scrubbing his arms, the surgeon put on a "sterile" hat and mask and then entered the operating room. Rubber gloves were worn only by the chief surgeon, the assistants wearing thin cotton gloves. The suture nurse worked without gloves.

After preparing the patient with soap, water and then alcohol, a single large rusty colored drape sheet was placed over him. No additional towels were placed around the proposed site of incision. The patient's feet remained exposed. This allowed for the intravenous administration of blood, plasma, saline or glucose. A doctor was in constant attendance supervising the administration of the fluid. Their technique of transfusion was somewhat unusual — the blood was poured into a wide open mouth flask and then allowed to remain until needed by the patient, at which time it was drawn up into a syringe and pumped into the vein. In contrast to American surgeons, they did not feel the necessity of beginning the intravenous fluids until the case was well under way and the patient in dire need—a conservative tendency was noted in all aspects of their surgery.

Endotracheal ether anesthesia was administered. The heat in the operating room was furnished by a large open tent stove in one corner. This, however, did not deter them from the use of ether. I anticipated an explosion or a fire — fortunately, the operation proceeded without event.

The surgical instruments did not occupy their usual place on a Mayo Stand, but were placed on the patient's legs. Their instruments vary considerably from ours — much lighter in construction and made of chrome rather than stainless steel. The entire operation was done with less than ten instruments. The suture material used throughout was white Japanese silk (between 00 and 000). All needles were of the French type and hence the suture nurse was able to work at a rather rapid pace. The lap packs and sponges were all old frayed cloths anchored with a hemo-

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stat. Bloody sponges were weighed for blood loss as done in many American institutions.

The procedure itself was probably a more limited cancer operation than one is accustomed to seeing in American surgical clinics. Even though somewhat conservative, it was technically an excellent operation. The procedure in its entirety was much shorter than those done in American hospitals, requiring only one and a half hours. An upper midline incision was made, no abdominal exploration was performed for metastases, and the stomach was removed without extirpating the spleen, greater or lesser omenta. An esophagojejunostomy was performed in the usual manner – a posterior layer of interrupted sutures was first placed and then the lumen of the jejunum was opened and the stomach cut off and a continuous over-and-over stitch was put in through the mucous membrane and carried around anteriorly (over-and-over instead of in-out and over). Interrupted silk was used on the anterior side as a final layer.

The duodenal stump was closed over a Payr clamp with an over-and-over running stitch with white silk. The stitch was then brought back as a second layer, without an attempt to invert the edges, however.

A jejunojejunostomy was then performed (side to side)—an open anastomosis using a continuous suture to both the mucous membrane and seromuscular layer. Instead of using a needle holder on these running stitches, a large curved atraumatic needle was simply manipulated adeptly by hand. Their anastomoses are done very rapidly and with facility, requiring an average of about eight minutes. All anastomoses are of the open variety.

A stomach tube is not a part of their armamentarium for gastrectomies (excepting in the presence of pyloric obstruction). No tube was employed preoperatively, nor was one inserted during or at the termination of the procedure. This to my mind violated a basic surgical concept, and added a potential hazard to the postoperative course. Intravenous feedings are employed for approximately four days, liquids are started on the fourth postoperative day and solid foods on the seventh day.

Early ambulation is practiced. Excepting this, no precautions are taken to avoid thrombophlebitis. The Japanese do not consider this a major complication as their incidence is rather low. A shorter life span and the notorious absence of obesity among the people may be two significant reasons for this difference.

One of the awesome features of the operation was the multitude of people in the room—nurses, doctors, medical students, orderlies, and observers, constantly walking in and out—all without the benefit of caps, masks or gowns. They are not convinced of the necessity of strict aseptic technique as practiced in the States. The low incidence of postoperative infection (5 per cent of cases) substantiates their claims.

We then made a tour of the hospital. A member of the family remains with the patient and does the cooking on stoves outside the ward; hence it is obvious that diets are little adhered to in Japanese hospitals. This member of the family does the duties of a private nurse. Throughout the wards very few patients were seen receiving intravenous fluids or blood transfusions. Although they employ inlying duodenal tubes to which suction is applied, and urinary catheter drainage in certain circumstances, no instances of their use were seen on the wards. The rubber tubing and bottles so familiar to our surgical wards were rarities in this institution. There is a skin glue which is employed by the Japanese in many cases instead of skin sutures. It is said to work rather well.

Thoracic surgery is done in only a minority of the large medical centers because anesthesiology is as yet a relatively new science here. The Kyushu University medical school didn't have an anesthesia machine until after the war. Prior to that they were limited to the use of spinal anesthetics, open drop ether or local procaine.

All in all it appeared that they were doing surgery in a rather simple, straightforward manner, without many of the intricacies and refinements which we employed. In other respects, however, they were quite progressive and approached that seen in American hospitals. The forte of Japanese surgery appears to lie in their dexterous operative technique.

Peritonitis and perforation of bowel may occur when ACTH is used in the therapy of ulcerative colitis. These complications with 1 death developed in 3 of 17 patients treated by Maurice Tulin, M.D., and Thomas P. Almy, M.D., of Cornell Medical Center, New York City, and Fred Kern, Jr., M.D., of Denver, after 25 mg. of ACTH had been given every six hours intramuscularly for seventeen to thirty days in 13 cases, and 20 mg. daily by infusion over an eight-hour period for two to fourteen days in 4.

J.A.M.A. 150:559-562, 1952.

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.*

Clinicopathological Conference

Minneapolis Veterans Hospital*

Edited by James F. Hammarsten, M.D.
Assisted by Robert I. Lubin, M.D. and
Donald Fry, M.D.

PRESENTATION OF CASE

A 57-year-old laborer was admitted on August 3, 1951, because of "dropsy" and shortness of breath for one month. The history was obtained from the wife since the patient had marked memory loss.

He was in good health until 22 months prior to admission when he noted tingling in his feet and hands and a staggering gait. He consulted a physician who told him that he had anemia and prescribed weekly liver injection and pills whose composition remains unknown. After three months the patient of his own volition discontinued the injections but continued taking the pills. During the following months he had rapid progression of numbness and tingling of the extremities and developed almost complete loss of coordination of the legs so that he was forced to use a wheel chair.

For one year he had intermittent swelling of the feet and ankles. One month before entering this hospital he had progressive swelling of the legs and abdomen with dyspnea and orthopnea. For two weeks he had occasional urinary and fecal incontinence. The week before admission he developed marked memory loss.

He became gray at the age of 21 years. He drank a gallon of beer daily supplemented with liberal but unknown amounts of whiskey and wine.

Physical examination showed an obese, pale, dyspneic, confused man with snow-white hair and blue eyes. There was bilateral arcus senilis. The tongue was normal. There were a few moist rales at both bases. The abdomen was protruberant. A fluid wave and shifting dullness were demonstrated. There was massive edema of the legs extending to the sacrum. The anal sphincter was atonic.

A neurological examination revealed moderate loss of strength in the arms and marked weakness of the legs. The patellar, ankle, abdominal and cremasteric reflexes were absent. The plantar reflexes were normal. Vibration sense was diminished below the iliac crest and absent below the knees. Position sense was diminished in the arms and absent in the legs.

The temperature was 99.4° F., the pulse rate 72 per minute, and the blood pressure 100 mm. Hg systolic and 70 diastolic.

The hemoglobin was 10.4 gm. per 100 ml., the red blood cell count 2,740,000 per cu.mm., the hematocrit 39 per cent, the MCD 8.6 μ, the MCV 142μ^3, the MCH 35.5$\mu\mu$, and the MCC 26.5 per cent. The white blood cell count was 8100 cu.mm. with 72 per cent neutrophils, 23 per cent lymphocytes, 2 per cent monocytes, and 3 per cent eosinophils. The smear of the peripheral blood showed marked anisocytosis and many macrocytes. Some of the red cells were stippled and there was an occasional nucleated red cell. There were numerous hypersegmented neutrophils with bright red granules. The reticulocyte count varied from 3.5 to 4.4 per cent. A blood Kahn was negative. The urinalysis was normal.

A blood urea nitrogen was 12.5 mg. per 100 ml. The serum protein was 7.4 gm. per 100 ml. with 4.8 gm. albumin and 2.6 gm. globulin. The bromsulfalein retention was 11.7 per cent in 45 minutes. The cephalin flocculation was negative in 48 hours. The thymol turbidity was 3.0 units, and the alkaline phosphatase 6 King-Armstrong units. The serum bilirubin was 0.1 mg. per 100 ml. in 1 minute and 0.7 mg. total. The cholesterol was 179 mg. per 100 ml. The prothrombin time was 14.5 seconds (control 13.5 seconds). The spinal fluid showed 436 red blood cells and 5 white blood cells per cu.mm., a protein of 47 mg. per 100 ml., a negative complement fixation test, and a normal gold curve.

X-ray films of the chest showed an area of atelectasis in the left lower lobe. A supine roentgenogram of the abdomen showed changes consistent with the presence of ascites. An electrocardiogram was normal. A bone marrow examination showed erythroid hyperplasia.

The vital capacity was 2.4 liters, the circulation time 13 seconds from antecubital fossa to tongue,

*Published with approval of Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

and the venous pressure 10 cm. of water. He was found to have residual urine of 700 cc. An abdominal paracentesis was done on the second hospital day but no fluid was obtained.

He was given a diet containing 200 mg. of sodium. By the fifth hospital day all the edema and rales had disappeared, but the patient was otherwise unchanged.

On the ninth hospital day, when being lifted from his bed to a wheel chair, he died.

DISCUSSION

DR. ROBERT HOWARD*: My discussion today will demonstrate the reasons why I was retired from clinical medicine to the field of medical education.

The patient to be discussed today had disease related to several body systems. We might as well begin with the question of the anemia. I had the privilege of reviewing the blood smears. There is definite macrocytosis and the neutrophils show hyperlobulation. The platelets appear decreased. What are the causes of macrocytic anemia?

The white hair developing at an early age and blue eyes suggest pernicious anemia. The gastric acidity was not determined. If achlorhydria were present, it wouldn't be very significant since alcoholics have a high incidence of achlorhydria. If free acid were present, it might alter my thinking.

Nutritional anemia is a possibility. The neurological changes would be unusual in that disease. There is nothing to suggest sprue. The macrocytic anemias of pregnancy and infancy are ruled out by definition. That more or less covers the megaloblastic anemias.

There are some other macrocytic anemias. Hemolytic anemias should be mentioned. The normal total reticulocyte count and normal serum bilirubin are arguments against a hemolytic process. Macrocytic anemia may occur in liver disease. He has every right to have liver disease and still the liver function tests are normal with the exception of the bromsulfalein. I can't recall seeing a macrocytic anemia with liver disease without more evidence of a diseased liver.

I get back to my original thought that the man had pernicious anemia. I also reviewed the bone marrow. The red cell series was normoblastic. It is possible that he had pernicious anemia, received liver extract, and then received a medication which may have been folic acid. We have seen a man with pernicious anemia who took a mail-order preparation containing vitamin B_{12} and folic acid and then had an exacerbation of the neurological complications. I wonder if this man was taking folic acid? This would account for the normoblastic bone marrow with progression of neurological findings. The neurological findings are consistent with subacute combined degeneration of the cord.

The edema is more difficult to explain. The intermittent edema would occur on the basis of prolonged sitting in a wheel chair. I don't believe the massive edema can occur on that basis. The normal serum protein and urine rule out renal edema. After all of these years of drinking, he could well have beriberi. The rapid circulation time would fit with that concept. With beriberi I would expect to find a peripheral neuritis.

Patients with pernicious anemia have an increased incidence of carcinoma of the stomach. It is conceivable that this man had a carcinoma of the stomach with peritoneal metastases and obstruction of the inferior vena cava by metastases. Such a process could produce ascites and edema. I don't like this explanation very well either. An extensive carcinomatosis should have affected his nutritional status. Another thought that occurred to me was pancreatitis with a large pseudocyst.

Every explanation of the edema that I have offered has something against it.

My final diagnoses are pernicious anemia, subacute combined degeneration of the cord, and perhaps carcinoma of the stomach with metastases to account for the edema and ascites.

DR. HELLER: What was the cause of his death?

DR. HOWARD: I was afraid someone would ask that. I suppose the most likely possibility in a man who had been bedridden for an extended period is peripheral venous thrombosis with a massive pulmonary embolus.

DR. HELLER: I certainly agree with Dr. Howard on the evidence for pernicious anemia with subacute combined degeneration, but I don't think there is enough evidence to say what the cause of the edema is. There is no evidence for cardiac or renal edema. I think the normal serum protein rules out nutritional edema and obesity would seem to exclude edema due to carcinomatosis. Edema may occur with severe alcoholism. There appears to be increased reabsorption of salt and water. The rapid clearing would fit with edema on that basis.

DIAGNOSES

Clinical diagnosis: Pernicious anemia with subacute combined degeneration of cord, hepatic cirrhosis, ? coronary arteriosclerosis, ? alcoholic neuropathy (neurological consultant).

Dr. Howard's diagnosis: Pernicious anemia, subacute combined degeneration of cord, ? carcinoma of stomach with metastases, ? pulmonary embolus.

Anatomical diagnosis: Pernicious anemia, subacute combined degeneration of the cord, atrophic gastritis. Mild chronic thyroiditis (of no apparent significance).

PATHOLOGICAL DISCUSSION

DR. GLEASON: I am afraid that we aren't going to add a thing to the explanation of the edema. We don't find it, and we find no anatomical cause for edema. There was no explanation for the sudden death. The stomach was thin and had no rugae present. Microscopically there was an atrophic gas-

(Continued on page 118)

*Assistant professor of medicine and director of postgraduate Medical Education, University of Minnesota.

Lancet Editorial

Minnesota Legislators and Health

Minnesota legislators have long shown their confidence in those properly trained for the promotion of good health by enacting laws and appropriating funds. On February 7, 1872 a bill was presented by members of the State Medical association for the establishment of a State Board of Health. The Legislature passed this bill, the following month, thus establishing the third State Board of Health in the United States. Later, the Legislature enacted laws creating local boards of health, and gave them the authority to quarantine domestic animals suffering from epidemic diseases.

In 1883 the State Constitution provided the privilege of creating a department of medicine at the University of Minnesota. Dr. C. N. Hewitt proposed to the Board of Regents that such a department be organized and a faculty of five members was appointed in January. Since no provision had been made for teaching, this first faculty served purely as an examining body. Up to that time a sizeable number of unqualified persons were practicing medicine in Minnesota and considerable quackery existed. The State Legislature came to the rescue and passed an act to regulate the practice of medicine, and required all physicians to be licensed. They also conferred upon the faculty of the department of medicine at the University the right to function as an examining board with power to approve and accept diplomas and to recognize certain medical colleges as evidence that their graduates were qualified to practice. The board could also request applicants to submit to board examinations. In 1887 the Legislature passed a new Medical Practice act and created an independent State Board of Medical Examiners. The same year, the University Board of Regents was petitioned to establish a qualified teaching department of medicine. Soon thereafter the private medical schools then in operation surrendered their charters and supported this proposed project. A teaching faculty consisting of 29 members was appointed and in October 1888 the first entrance examinations for students were held.

No medical building had been provided on the campus, so the faculty occupied a leased building at the corner of Sixth Street and Ninth Avenue South. However, an appropriation was made whereby a small building known as Medical Hall was constructed on the campus in 1893, and two years later the laboratory of the Medical Sciences building was added.

Ever since these early days legislators have generously supported building programs. Their loyal support, together with donations from individuals and organizations, has brought about the Mayo Memorial building now under construction.

The Medical School increased its teaching faculty from 29 in 1888 to 114 twenty years later, and to over 500 in 1953.

Although the Legislature provided for a College of Veterinary Medicine in 1891, the proposal did not succeed because there was no demand. Veterinary medicine had become a part of the curriculum in the School of Agriculture on March 6, 1888. In 1893 the division of Veterinary Medicine was created. The chiefs of this division did excellent work from 1893 to 1947. Dr. W. L. Boyd, who was then chief, became director of a complete and excellent School for Veterinary Medicine which had been authorized by the Legislature. With Dr. Boyd's retirement, Dr. M. H. Roepke became director in July 1952.

In 1903 the Legislature passed an act to establish a State Livestock Sanitary Board. All authority which had previously been conferred upon the State Board of Health concerning infectious diseases among animals was transferred to this newly created board.

Thus, since 1885 when the Legislature passed an act conferring upon the Board of Health power to quarantine domestic animals suffering from epidemic diseases, Minnesota legislators have approved practically every well-recommended procedure to protect animals against diseases which previously had been so destructive among them. Particular emphasis was placed on the control and eradication of those animal diseases transmissible to people. Our legislators won a great victory in enacting laws and appropriating funds to protect animals. For example, rabies and glanders, said to be the most horrible of all diseases which attack both animals and people, have been brought well

under control. In fact, glanders has been eradicated from Minnesota. While minor outbreaks of rabies occur occasionally among animals they are usually brought under control promptly. The last human death from this disease occurred in 1917. Anthrax has become exceedingly rare among our animals and people. Tuberculosis, which caused such losses among various species of animals early in this century, and was so frequently transmitted to people, has been so reduced among cattle that now only one in 5,000 animals has been infected with this germ. Those who are directing the present attack on brucellosis are winning the fight. Suffering from disease among animals has been reduced to a minimum.

While our legislators made provisions for the pleasant existence of animals, they also supported the use of animals in obtaining knowledge beneficial to other animals and people. On many occasions misinformed or uninformed individuals have become emotional or even fanatical about the use of animals for the study of the effects of drugs, surgical procedures, etc., and have presented bills for legislative action prohibiting their use. Such bills have been defeated by our legislators. To have passed any one of them would have nullified or seriously interrupted the program designed to improve the health of both animals and people.

Most physicians are fond of pets — particularly dogs. They employ veterinarians for their dogs just as they do physicians for their children. When the veterinarian corrects the defects, sets broken bones, or controls disease, much of his knowledge which enables him to do his work successfully came from experiments on animals in schools of veterinary medicine and elsewhere. Without such experiments veterinarians would be far less helpful to the pets of today. Much of the fine health work done so successfully on domestic animals is the result of knowledge obtained from experimental animals.

Studies consisting of experimental work on animals have resulted in knowledge which when applied to humans has prevented much illness and many untimely deaths. Several of our present-day drugs were first administered to animals to determine not only effectiveness but also toxicity. When found to be safe for animals, these drugs were cautiously administered to people until dosage could be properly standardized. The so-called "miracle drugs," including the sulfonamids and the antibiotics, are good examples. They were first given to animals, and those found to be ineffective or too toxic were either modified or eliminated. The ones which proved helpful and harmless to animals were safely given to people, and those found efficacious, such as penicillin and streptomycin, are now in common usage. It is said that the discovery of penicillin and the subsequent antibiotics have added ten years to the span of man's life on earth. Experimental animals contributed greatly to this accomplishment. Numerous other preparations are now being studied in the same manner and doubtless still others will follow, some of which most likely will effectively control disease.

Animals themselves are now benefitting significantly from standard drugs such as antibiotics. Veterinarians use them extensively and save numerous lives of nearly all species of animals, including pets suffering from infections such as pneumonia.

Prior to the advent of insulin about 30 years ago (1922) literally hundreds of millions of people in the world suffered and died from diabetes. Dogs were required in the experimental work of Banting et al. in the production of insulin. The million or more persons now living in this country who have diabetes are not doomed to a lingering death but are able to lead reasonably normal lives because of insulin. This has been the plight of literally hundreds of millions of persons in the world since insulin became available and affords the same sure relief for future generations.

Prior to the work of Murphy et al. (1926) pernicious anemia was a universally fatal disease. Tremendous numbers of persons throughout the world had died from this condition over the centuries. Murphy and his coworkers used dogs to develop a simple, direct and effective treatment consisting of whole liver, liver extract, or ventriculin. Since this treatment has been available, persons with pernicious anemia can live indefinite periods without discomfort provided they are conscientious about adhering continuously to the treatment.

More than a century ago, the first general anesthetic to be studied was ether. It was first used on dogs, and when a safe method was developed in this manner it was employed among people. A number of general anesthetics have since been developed which first were studied experimentally on dogs. These anesthetics whose safety and effectiveness dogs helped so much to determine are now employed not only in humans, but also in experiments on dogs. Without anesthesia much modern surgery would be impossible.

Because so much experimental work has been

done on dogs their anatomy and physiology are well known, and the surgeon can proceed with research projects knowing what to expect from the various organs and systems in this animal's body. Dogs manifest so much confidence in people and are so docile that they submit to experimental procedures better than any other animal.

The dog has contributed tremendously to successful surgery in people. Practically every important surgical procedure performed today was learned in experimental laboratories on dogs. This is true of approximately two dozen life-saving operations done in different parts of the abdomen alone. The delicate techniques employed in brain surgery were learned for the most part on dogs.

Within the past 20 years surgeons have learned how to successfully remove diseased lungs, lobes and smaller units, thus completely curing such conditions as cancer, abscess, bronchiectasis, etc., and aiding greatly in the treatment of tuberculosis. Techniques for these operations were for the most part learned on dogs.

The department of surgery at the University of Minnesota has made many fine contributions by way of modified and new operations, all of which have first been studied carefully on dogs. The most recent outstanding contribution was the successful closure of an atrial septal defect in a child with the aid of hypothermia. The experimental work on dogs consisted of gradually lowering normal rectal temperature of 38° C. and a pulse rate of 160 to 180, to a temperature of 26 to 28° C. and a pulse rate of 50 to 70. All vessels to and from the heart were then obstructed, the right atrium was opened, and any remaining blood was evacuated. A large defect through which the index finger could be introduced was produced by removing a part of the membranous septum. After the operation was completed the animal's body was rewarmed. In due time the chests of the surviving animals were reopened and the septal defects repaired. Twenty-seven of the original 39 animals survived the production of atrial septal defects. Twenty-six were later subjected to the operation for closure of septal defects. In one which had been operated two and one-half months earlier the defect was found to have healed; four died during anesthesia or during the cooling process before the heart was opened. In the remaining 21 the septal defects were closed; 17 of these survived the surgery. When these 17 animals were later sacrificed, all of the septal defects were found to be soundly healed.

Most of the deaths that occurred in this experiment were in the early days of the work. These experiments led to such improvement of technique that the operation rarely failed. For example, among the last 10 attempts to produce septal defects there was only one death, and only one occurred among the last 10 operations which closed the defects. Thus in these experiments the surgeons learned how to prevent or control such complications as coronary air embolism, and ventricular fibrillations not related to air embolism.

If it had been necessary to develop this safe technique on children, it is probable that approximately 20 out of 39 would have died. However, the technique of the operation was so perfected on dogs that on September 2, 1952 a septal defect was successfully closed in an underdeveloped, sickly five-year-old child weighing only 29½ pounds by essentially the same technique that had been so well developed on dogs. This child's body was cooled to 82° F. (rectal) and the cardiac inflow was occluded for a total of five and one-half minutes, during which time the septal defect, approximately two centimeters in diameter, was closed under direct vision. At the end of the operation, which lasted only 58 minutes, rectal temperature was only 79° F. She was placed in water at 113° F. and within 35 minutes the rectal temperature registered 96.8° F. She promptly recovered from the anesthesia and her convalescence was uneventful.

Many of the great accomplishments from which humans and animals themselves have benefited so much could not have been made if physicians had been compelled to do only non-survival experiments. Throughout the entire history of this work, so-called chronic experiments for which animals are kept alive for varying lengths of time were absolutely essential in order to determine the effectiveness of various procedures and the safety of certain techniques.

The dog is often spoken of as man's best friend. Many dogs in daily life have sacrificed their lives attempting to protect their masters; they have stoutly defended their country in war. Dogs show unusual satisfaction and seem to be happiest when they are helping people. In the work about a farm, a well-trained dog may practically take the place of a person in tending domestic animals, doing errands, guarding the premises against intruding animals and thieves, and ever befriending and comforting members of the family. Even in the experimental laboratory after becoming acquainted with the staff, the dog exhibits a friendly and cooperative spirit.

Staff members become fond of experimental dogs and a spirit of mutual helpfulness prevails. Certainly these animals, who have so befriended man, would not want to be denied the privilege of contributing to medical and surgical progress. By participating in laboratory experiments they contribute to the good of man as well as to the welfare of their own species.

Throughout the years Minnesota legislators have familiarized themselves with facts about promoting all phases of good health and have acted accordingly. Now they have to their everlasting credit a record of health improvement which has given to Minnesotans greater efficiency, and happier and longer lives.

Present-day research is working toward the control of the remaining prevalent and highly fatal conditions, such as cancer, the leukemias and various heart diseases. But much more needs to be done. With good administrators, highly-trained scientists and physicians, adequate buildings with well-equipped laboratories and hospital facilities, the solution of some of these problems seems assured. Such a hopeful future can be achieved only by training young men and women to assist and later to assume full responsibility. Today, this is being accomplished by the school of medicine and the closely related scientific departments which our legislators have supported so admirably. J. A. M.

The Continuation Medical Education Program

A PHYSICIAN'S EDUCATION, like woman's work, is never done. The really competent physician will not be satisfied to practice 1951 medicine in 1953; nor will he be content to practice 1953 medicine in 1955. Today's rapid advances in the fundamental sciences and in the diagnosis and treatment of disease will serve to make him aware that his graduation from medical school represented not a climax in the story of his professional life but only the end of the prologue.

Several means are at his disposal for accomplishing this process of lifelong education. He will read extensively in various medical periodicals. He will attend meetings of the local, regional and national medical societies of which he is a member. He will probably also attend, at intervals, postgraduate or continuation courses which are offered in a large number of centers throughout the country. From a great variety of courses, he will be able to select those which satisfy his needs and interests.

At the University of Minnesota, the continuation medical education program was initiated in 1937 under the guidance of the late Dr. William A. O'Brien. With wisdom and foresight, with an intense personal interest in the project, and with the cooperation of the entire medical school faculty, he established the program on a solid foundation. The Center for Continuation Study provided then as now, unique facilities for postgraduate medical teaching.

Following World War II the program was greatly expanded in order to meet the needs of physicians released from military service. This expansion was made possible in large part through the generous support of the W. K. Kellogg Foundation. From 1945 to 1949, 511 physicians, mostly veterans, attended basic science courses of three to nine months' duration. In addition, the presentation of shorter courses in clinical subjects continued throughout that period. By 1949 demand for basic science courses had largely been satisfied, and since then only the shorter type of program, designed for the physician in active practice, has been offered.

Following Dr. O'Brien's untimely death in 1947, Dr. George N. Aagaard was appointed director of the department, then known as the department of postgraduate medical education. His able leadership resulted in continued expansion of the activities of his department including the introduction of a series of regional seminars presented in various areas throughout the state. At the time of his resignation at the end of 1951 to accept the Deanship at Southwestern Medical School, Dr. Aagaard was a recognized authority in this field.

At the present time the University, through the department of continuation medical education, offers from 20 to 25 courses each year at the Center for Continuation Study. All but four or five of these are intended primarily for physicians engaged in general practice. During the year 1951-52 over 900 physicians attended 21 courses at the Center. Many other physicians attended regional seminars as well as postgraduate courses offered elsewhere. We believe that the physicians of the Upper Midwest are convinced that programs of this type are of value to them in solving the problem of how best to keep abreast of advances in medicine without having to neglect their active and demanding practices.

ROBERT B. HOWARD, M.D., *Director, Department of Continuation Medical Education, University of Minnesota*

The Architecture of Normal and Malformed Hearts, by MAURICE LEV, B.S., M.D. and ALOYSIUS VASS, M.D., 1951. Springfield, Illinois: Charles C Thomas, 142 pages.

This monograph presents the biogenetic law as it applies to the development of the human heart and as presented by Dr. Alexander Spitzer. Because of the complex nature of the problem and the intimate knowledge of embryology required this monograph is of primary interest to cardiologists and to cardiac surgeons. Spitzer's theory is difficult to comprehend but those interested in this field should find considerable stimulation in correlating the embryological anomaly and the clinical findings.

The primary value of this monograph lies in the fact that it presents to the American medical field the first adequate translation of Spitzer's work. W.P.E.

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Inter-Allied Conferences on War Medicine convened by the Royal Society of Medicine, 1942-1945, honorary editor MAJOR-GENERAL SIR HENRY LETHEBY TIDY, 1947. 531 pages. London: Staples Press Limited, Publisher.

This volume contains the reports delivered at the conferences held by the Medical Services of the Allies stationed in Great Britain between 1942 and 1945 and sponsored by the Royal Society of Medicine of London.

Included are reports which concern all aspects of the application of the practice of medicine to war. Problems of organization, surgical treatment, neuropsychiatry, blood transfusions, and venereal disease, general medicine and tropical diseases are discussed.

Of special interest are the reports of personal experiences in famous epics such as Dunkirk, the Arctic Convoy to Russia, and Buchenwald. G.K.

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Infrared Radiation Therapy Sources and Their Analysis with Scanner, by LEOPOLD ROUNER, edited by OTTO GLOSSER, Ph.D., 1950. 33 pages, 21 illustrations. Springfield, Illinois: Charles C Thomas.

This monograph discusses the measurement of infrared radiation with infrared Scanner instrument. Conclusions are drawn from this study on the proper selection of lamps for therapeutic purposes and uses. P.K.

Early Care of the Seriously Wounded Man, by HENRY K. BEECHER, M.D., chief, department of anesthesia, the Massachusetts General Hospital, Boston, Massachusetts, 1952. A monograph in the American Lectures in Surgery. 32 pages. Springfield, Illinois: Charles C Thomas. seventy-five cents.

The principles and procedures concerning the treatment of the wounded in World War II are the basis of experience for this book. It is mainly concerned with the crucial interval from the instant the patient is wounded until the surgeon repairs the wound. The author also stresses the general principles of resuscitation which need emphasis and gives the reader the benefit of wide experience in this field. He emphasizes the speed in forward evacuation and preparation for surgery of the patient and that the most efficient resuscitation is preventive. He points out that emergency surgery, whether civilian or military, is little if any more hurried than elective surgery. No surgery should be performed unless shock has definitely been prevented or the good condition of a shock patient has been restored, although it is nearly always necessary to initiate the surgical procedure long before the consequence of shock can be fully overcome. The operation ought then to be undertaken as soon as experience has shown the patient will tolerate it, the author using the following criteria – chiefly a rising blood pressure (85 mm. of mercury or above), a falling pulse rate, a warm skin and good color of the mucous membranes. The surgeon in the field, however, may be confronted with the necessity of undertaking an operation with the patient in a poor condition.

The next chapter tells how to make it possible for all severely wounded men to withstand evacuation from the site of wounding to the installation where initial surgical measures can be undertaken, and how to support him through stresses imposed by transportation, anesthesia, and operation. The specific preoperative procedures at the installation where initial surgery will be undertaken are listed. They do not deviate from any emergency admission at a civilian hospital for a patient who is in impending shock or a shock patient for whom an emergency operation is indicated.

A few good practical points in the care of men with specific wounds are given. The chapter on the use of analgesics and preoperative medications is excellent. The indications and contraindications of morphine are stressed, the intravenous administration of morphine being the route of preference.

As for the maintenance of anesthesia of the wounded men, he again calls attention to two drugs, atropine and pentobarbital sodium, as being of real importance in preanesthetic medication.

Of the inhalation anesthetics, he emphasizes that ether is the choice in the seriously wounded particularly for major thoracic surgery, abdominal surgery, and caring for compound fractures of the femur, and in all procedures which are estimated to take one-half to one hour or more. For minor procedures, nitrous oxide inhalation, local anesthesia, or intravenously given thiopental sodium are the anesthetics of choice. Spinal anesthesia is never acceptable for men recently and seriously wounded.

The general principles as well as the specific procedures described in this book are based upon experience gained on the battlefield and as military medical experience but it is presented in a way to benefit also all civilian surgeons. E.L.

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Manual Therapy, For student and practicing physician, by JAMES B. MENNELL, M.D., editor, W. A. SELLE, Ph.D., 1951. 64 pages, 10 illustrations. Springfield, Illinois: Charles C Thomas. $2.25.

A brief and succinct discussion of various methods of manual therapy are included. Various forms of massage are discussed, such as cupping pressures. Also passive movements, assisted movement and resisted movements are defined and their uses explained. Lastly some basic theory and practice is discussed on joint manipulations. P.K.

American College Health Association News . . .

The Executive Committee has approved the applications for membership of the following two institutions:

Lebanon Valley College, Annville, Pennsylvania, with an enrollment of 325 men and 150 women undergraduate students. Dr. James R. Montcith is the part time physician on the Student Health Service staff, and the two full time nurses are Miss Arlene Snyder and Miss Janice Delong. Lebanon Valley College is accredited by the Middle States Association of Colleges and Secondary Schools, the National Association of Schools of Music, and the State Department of Public Instruction.

Sacramento State College, Sacramento, California, with an enrollment of 1,087 men and 1,076 women undergraduate students. The staff of the department of health and physical education includes: the director, Dr. Donald Bailey; Dr. Herbert McCormick; Dr. Frank B. Jones, who serves as health educator and sanitarian; Dr. Tobin, part time physician; and Mrs. Helen Gilkey, the full time nurse. Sacramento State College is accredited by Northwest Association of Secondary and Higher Schools, Western College Association, and the State Department of Education.

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The *Illinois Section* of the ACHA held its annual meeting November 15, 1952, at the University of Chicago. Dr. William Lester of the University of Chicago welcomed the guests, and Dr. Otto Keller, president of the Illinois Section, made a few opening remarks. The following papers were presented:

"Hypothyroidism in Early Adult Life"—Dr. Richard Landau, associate professor of medicine, University of Chicago

"Report on Boston Meeting"—Dr. Leona Yeager, director of the student health service, Northwestern University

"Legal Problems Related to the Exchange of Medical Records and Information"—Mr. Griffin, attorney, DePaul University Law School

"Acute Respiratory Infections at the University of Chicago, 1951-1952"—Dr. Walter Hawk, assistant director of the student health service, University of Chicago

"The Differentiation between Organic and Functional Heart Murmurs"—Dr. Walter Brill, physician, student health service, University of Chicago.

The following slate was elected for the year 1952-53: President—Dr. H. L. Lawder, University of Illinois; vice-president—Dr. William Lester, Jr., University of Chicago; secretary-treasurer—Mrs. Raidie P. Mitchell, R.N., Roosevelt College; council at large—Dr. S. C. Udell, Roosevelt College; Dr. L. M. Dyke, University of Illinois.

The meeting closed with an open house at the Student Health Service of the University of Chicago.

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At a meeting in New York in December about twenty persons representing several national associations decided to hold a Fourth National Conference on Health in Colleges in 1954 in New York City. Dana L. Farnsworth, M.D., was selected conference chairman and chairman of the planning committee.

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The Association regrets to report that Dr. Reid White, who was the beloved university physician for twenty years at Washington and Lee University, died on December 4, 1952.

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Drs. Irvin W. Sander, Wayne University, chairman, and Norman Moore, Cornell University, whom President Durfee appointed to continue the study of a training program of physicians interested in student health work, have submitted a tentative program to four universities for study and possible approval. The special committee plans to submit this proposal in its final form to the members of the Association at the Columbus meeting. If it is approved, several universities will initiate the program in September as a pilot study to determine how much demand there is for such a program and whether or not it can be worked out in the varying situations found in different schools.

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Mrs. F. E. Fruvog, R.N., Director of Student Health Service at Hamline University, reports that the Ramsey County Tuberculosis Association and the State Department have cooperated in sending a mobile unit for miniature x-rays to the campus. The program has been highly successful, with both students and other individuals on the campus participating in the campaign. One of the health education classes under the leadership of Mr. Clarence Nelson, instructor, has been responsible for a great deal of publicity, organization, and detail work. The speech department has also cooperated by training certain students to talk to groups on the campus, such as fraternities and dormitories, in an attempt to popularize the program. A blood mobile unit was also on the campus, and a program for blood donations was carried on in a similar fashion.

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New delegates of member institutions are:

Sanford E. Ayers, M.D., director, student health department, University of Florida, Gainesville, Florida.

Fred A. Feddeman, M.D., university physician, Washington and Lee University, Lexington, Virginia.

Samuel E. Hoke, M.D., college physician, Allegheny College, Meadville, Pennsylvania.

Ray E. Watts, A.M., director of physical education and health, Baldwin-Wallace College, Berea, Ohio.

Ralph G. Harshman, Ph.D., dean of administration, Bowling Green State University, Bowling Green, Ohio.

E. D. Lovett, M.D., health officer, California State Polytechnic College, San Luis Obispo, California.

Barbara C. Gurd, M.D., head of health education department, Radcliffe College, Cambridge, Massachusetts.

Claire K. Amyot, M.D., college physician, Skidmore College, Saratoga Springs, New York.

Glenn West, M.D., student health service, State College of Washington, Pullman, Washington.

W. R. Nesbitt, M.D., director, student health service, University of Wyoming, Laramie, Wyoming.

James L. Weiler, M.D., director of student health service and college physician, Knox College, Galesburg, Illionis.

George X. Trimble, M.D., director, student health service, University of Missouri, Columbia, Missouri.

F. B. Cotner, Ph.D., dean, Division of Science, Montana State College, Bozeman, Montana.

News Briefs . . .

North Dakota

CANDIDATES who recently passed the examinations given by the North Dakota state board of medical examiners have been announced by the board. Successful candidates and the cities in which they plan to practice include Dr. Freddie Nadine Peterson, Bismarck; Dr. James F. Harrington, Jr., Mandan; Dr. Oscar Domke, Dr. Harry F. Cooper, and Dr. Frank A. Vesey, Minot. Other successful candidates who qualified by reciprocity are Dr. Martin H. Swerling, Bismarck; Dr. Olive E. Pitkin and Dr. David B. Horner, Minot; Dr. John E. Sweeney, Fargo and Dr. John W. Denser, Bowman. Secretary-treasurer of the state board is Dr. J. Glaspel of Grafton.

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DR. WILLIAM F. NUESSLE, who has been associated with the Dakota clinic in Fargo, has been called to active duty with the Air Force. He is now stationed at the Rapid City, S. D., Air Force Base in general practice.

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NEWLY-ELECTED CHIEF of the medical staff at St. Aloysius hospital in Harvey is Dr. P. A. Boyum while Dr. Charles J. Beck has been elected secretary. Other members of the staff are Dr. Francis W. Ford, Dr. A. F. Hammargren, and Dr. B. Hordynski of Drake; Dr. D. W. Mathaei of Fessenden and Dr. L. E. Boyum of Harvey.

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THE newly-built Kulm Community Health Center is now the location of the offices of Dr. J. E. Grenz. Residents of Kulm have been urged to visit this recently-completed community project.

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THE Board of Administration in Jamestown has announced the appointment of a clinical director for the North Dakota state hospital. He is Dr. Thomas L. Gore, formerly a staff physician at the Camarillo state hospital, Camarillo, Calif. Dr. Gore retired from the Army Medical Corps in 1939 after 22 years of service. Since that time he has been engaged in private practice and also served on the staff of a veterans hospital in Albuquerque, N. M. Dr. Gore is a graduate of the University of Pennsylvania Medical School, the Army Medical School, Washington, D.C., the Army School of Aviation Medicine, and the Army Field Service School.

* * *

THREE PHYSICIANS have been named as officers of the medical adivsory board of St. Michael's hospital in Grand Forks. They are Dr. R. W. Vance, president of the board, Dr. Nelson A. Youngs, vice-president, and Dr. E. A. Haunz, secretary-treasurer. Dr. Vance also has been appointed chief of staff, succeeding Dr. W. H. Witherstine whose term expired.

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THE new St. Gerard Community hospital was dedicated recently at Hankinson, which is about 75 miles south and west of Fargo. The hospital will accommodate up to 20 patients and was built at an estimated cost of $125,000.

* * *

DR. JOHN F. JOHANNSON, formerly of Kenmare, is now located in Cavalier, taking over the practice of the late Dr. George Waldren.

Minnesota

THE Minnesota State Medical association has presented its first annual $1,000 medical scholarship to Richard Engwall of Winthrop. The scholarship provides that same sum annually for four years of training with the recipient agreeing to practice medicine in a town of 5,000 population or less for five years after graduation. The award was presented at the annual County Officers' meeting of the association in St. Paul by Dr. F. J. Elias, Duluth, chairman of the scholarship selection committee. The state medical association plans to present an additional four-year scholarship each year until a total of four have been given.

* * *

A TOTAL GRANT by the U. S. Public Health Service of more than $70,000 has been given to the University of Minnesota for a three-year study to determine cause of certain neurological disorders. Director of the research project will be Dr. A. B. Baker, head of the division of neurology.

Other grants include $33,333 for scholarships in psychiatric nursing; $30,000 to Dr. Ancel Keys to continue research on the role of diet in heart disorders; $42,950 to Dr. Lewis Thomas for two projects in heart research, and $20,000 to Dr. Dennis Watson for a rheumatic fever study.

* * *

A NEW 25-bed psychiatric center for children has been established at the University of Minnesota. It will be an extension of outpatient psychiatric service for children set up in 1938. Previously, however, hospitalization had been only in psychiatric units for adults or in pediatrics sections. Dr. Reynold Jensen, professor of pediatrics, will be medical director of the unit.

* * *

MACALESTER COLLEGE dedicated its new Winton health center in February with Dr. Wallace P. Ritchie, St. Paul surgeon and a Macalester trustee as speaker. A tour of the health center followed.

* * *

DR. LEO G. RIGLER, professor of radiology at the University of Minnesota, has been named to a team of 15 medical scientists who are to go to India at the request of the Indian health ministry. The team will advise doctors there on the latest medical knowledge. The group is jointly sponsored by the United Nations World Health organization (WHO), and the Unitarian Service committees. Dr. Rigler, who previously went on a similar mission to Japan, is among five Americans on the team.

* * *

AN AILING Minnesota newspaper is looking forward to a new life thanks to the efforts of a Rochester heart specialist. The paper is the Mantorville *Express,* almost as old as Minnesota itself, and the publisher is Dr. H. L. Smith, retired after 27 years in the cardiology department of the Mayo clinic. Also called in on the case is Dr. James Eckman of the publications department of the clinic who will provide technical advice. Both men count printing and type collecting as hobbies of many years standing.

* * *

DR. J. ORWOOD CAMPBELL, clinical professor of surgery at the University of Minnesota, assumed office on January 1

as president of the Minnesota State Medical Association. He will preside over the centennial celebration of the founding of the organization in 1853, scheduled later this year.

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DR. WESLEY SPINK, professor of medicine at the University of Minnesota, is one of ten doctors to receive awards for distinguished achievement for 1953 from *Modern Medicine*. Spink was cited for leading the development of treatment for brucellosis and means of preventing the disease.

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DR. HOWARD R. HARTMAN, who recently retired as senior consultant of the clinical section of the Mayo clinic has been retained as consulting physician for the Chrysler Corporation.

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DR. SIDNEY O. HUGHES of Mandan, N. D., has joined the staff of the Winona clinic at Winona, Minn., practicing internal medicine.

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DR. L. B. MOYER has moved to Belgrade where he will be affiliated with a clinic. He formerly practiced in Lake Preston, S. D.

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NEW HOSPITALS in Minnesota include the $2,500,000 St. Francis hospital at Breckenridge with 126 beds, serving the cities of Breckenridge, Wahpeton, North Dakota, and Wilkin and Richland counties. Also dedicated is the $825,000 St. Francis hospital at Shakopee.

South Dakota

DR. M. C. ROUSSEAU was elected chief of staff at St. Ann hospital, Watertown. Dr. G. Robert Bartron was elected vice president and Dr. Donald Olson, secretary. New heads of departments are Dr. H. Russell Brown, department of surgery, Dr. O. S. Randall, department of clinical pathology; Dr. C. Rodney Stoltz, department of obstetrics; Dr. John Argabrite, department of x-ray; Dr. Carroll Clark, department of medicine, and Dr. Mary Schmidt, department of pediatrics.

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DR. F. J. TOBIN was named president of the Methodist State Hospital staff at their recent annual election. Other officers are Dr. R. J. Delaney, vice-president, and Dr. E. C. Bobb, secretary.

* * *

A RESEARCH GRANT of $17,500 was awarded to Dr. Earl B. Scott, associate professor of anatomy in the school of medicine of the University of South Dakota. This makes a total of $30,700 awarded to Dr. Scott by the USPHS of the National Health Institutes in the last three years. Dr. Scott's study deals with the histo-pathological effects of amino acid deficiencies.

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A FIRST-HAND ACCOUNT of medical service in England was made available to members of the Yankton District Medical society a few weeks ago when Dr. John H. Fodden from England spoke on the subject "The Socialistic Medical Service of Great Britain." Dr. Fodden left England in 1948 and is now at the University of South Dakota in Vermillion.

DR. C. O. MC PHAIL of Crosby has been elected president of the Kotana District Medical society. Other officers include Dr. P. O. C. Johnson of Watford City, vice-president, and Dr. Donald E. Skjel, of Williston, secretary-treasurer.

* * *

COMMUNITY COOPERATION, sparked by the earnest efforts of the women's auxiliary of the Tri-State Memorial Hospital association, pushed toward completion the plans for the hospital's formal opening. Built at a cost of $40,000, the women raised the necessary working capital of $7,000 in three days time. Dr. J. M. Hermanson will be resident doctor at this Valley Springs hospital.

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DR. LEONARD TOBIN was named chief of staff of St. Joseph's hospital in Mitchell, recently. Officers chosen were Dr. Donald Mabee, vice-president, and Dr. W. A. Delaney, Jr., secretary.

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DR. FRED LEIGH of Huron was presented with the 1953 distinguished service medal of the South Dakota Junior Chamber of Commerce.

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DR. ALFRED B. SCALES of Pickstown has voluntarily reentered the Army Medical Corps and is now post surgeon and hospital administrator at Fort Benjamin Harrison, Indianapolis, Ind.

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DR. STANLEY W. FOX, formerly of Clear Lake, is now located at Pierre.

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NEW to Belle Fourche is Dr. Edward Hanisch who has joined the staff of the Belle Fourche Medical Center. He formerly practiced in St. Paul, Neb.

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DR. MICHAEL SPIRTOS has joined the staff of the Yankton Clinic.

* * *

FIVE NEW MEMBERS have been appointed to the faculty of the school of medicine at the University of South Dakota. They are: Dr. F. E. Kelsey, professor of pharmacology and chairman of the department of physiology and pharmacology; Dr. Max A. Henrich, assistant professor in pharmacology; Dr. J. H. Fodeen, associate professor in the department of pathology; Dr. E. C. Pirtle, assistant professor in microbiology, and John Heemstra, instructor in the department of microbiology.

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DR. KARLOS ZVEJNIEKES was welcomed to his new practice in Hosmer by a community reception. He came to the United States from Latvia. Another newcomer is Dr. Rudolf Orgusaar, a native of Estonia who has opened an office in Revillo. The community has been awaiting his arrival for nearly a year while he completed his internship in Sioux Falls. Previously, Dr. Orgusaar graduated from medical school at Alexander university in Germany.

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DR. R. V. ROGERS formerly of Cody, Wyo., has now opened an office in Broadus. His coming was in response to a community appeal for medical services in that area.

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DR. SIDNEY F. BECKER has recently become associated with the Madison clinic in Madison.

NEWS BRIEFS—(Continued)

Other new locations and appointments . . .

Dr. Everett Harris, Marion, Illinois and Dr. Charles Price, Santa Monica, California, both to Chamberlain. . . . Dr. Stephen S. Aldridge, Minneapolis, to post as chief surgeon of the Veterans Administration Center at Hot Springs. . . . Dr. A. Privka, Sioux Falls, to a new practice in Kennebec.

Iowa

Dr. James R. Weeks, associate professor of pharmacology at Drake university, has been awarded a research grant of $3,618 by the U.S.P.H. for development of a respirameter vessel for studying oxygen consumption of isolated muscle. Research will be done at Drake over the next two years, with another grant to be issued next year.

Wisconsin

The new $450,000 Hudson memorial hospital was dedicated in ceremonies on Sunday, January 11. The hospital, opened recently, has 32 beds, eight private rooms and 18 service rooms with examination, surgical and laboratory facilities. Dr. Owen H. Wangensteen, chairman of the department of surgery of the University of Minnesota, spoke at the ceremonies.

* * *

Dr. Arnold S. Jackson, chief of staff at the Jackson clinic and Methodist hospital, Madison, Wisconsin, was elected president of the United States chapter of the International College of Surgeons at their recent meeting in Chicago.

Deaths . . .

dr. william a. coventry, 76, obstetrician and gynecologist, died recently in a Duluth hospital. He retired from practice in 1951, closing a medical career which began 51 years before. Dr. Coventry had delivered more than 5,200 babies in Duluth. Holder of the Minnesota Medical association's distinguished service medal, Dr. Coventry was named one of the state's 100 greatest living men in 1949 by the Minnesota Junior Chamber of Commerce.

* * *

dr. john s. macnie, 78, a long-time associate professor in the University of Minnesota medical school died in Minneapolis January 30. At the time of his death he was engaged in private practice as an eye, ear, nose and throat specialist. He received his medical degree at Columbia university in 1896. Dr. Macnie opened his Minneapolis practice and joined the university medical staff in 1904 after graduate studies in London and Vienna.

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dr. m. o. oppegaard, 67, a founder of the Northwestern clinic at Crookston, Minn., and a former mayor of that city died January 22. He was considered a pioneer in chest surgery in the Crookston area. Dr. Oppegaard graduated from the University of Minnesota in 1910 and attended Chicago Polytechnic clinic, New York Post Graduate hospital and Massachusetts General hospital at Boston.

* * *

dr. carl l. larsen, 71, St. Paul eye, ear and nose specialist and past president of the Ramsey County Medical society died January 29. He was graduated from the University of Minnesota medical school in 1904 and began his practice in St. Paul in 1910. He practiced until his death.

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dr. w. e. richardson, 80, of St. Paul, who practiced in Minnesota and South Dakota more than 50 years died February 7. A native of Elgin, Minnesota, he received his medical degree from Rush Medical college, Chicago, and started his practice at Slayton, Minnesota, where he stayed for 21 years. Pipestone, Minn., Philip, S. D., and Rushford, Minn., were other localities where he subsequently practiced. After his retirement he held a position for three years as plant physician for Morrell & Co. in Sioux Falls, S.D.

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dr. arthur s. watson, 32, died at his Robbinsdale, Minnesota home January 21.

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dr. a. a. schultz, 65, retired Fort Dodge, Iowa physician died January 12 at Veterans hospital in Des Moines where he had been a patient since last summer. Dr. Schultz practiced in Fort Dodge for nearly 38 years when he retired in 1951. He obtained his medical degree from Northwestern University. He was a veteran of World War I. On retirement, Dr. Schultz was the second oldest active physician in point of service in Fort Dodge.

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dr. a. l. haynes, 84, pioneer West River physician died in Bismarck, N. D., January 28, after an illness of several weeks. Prior to his retirement eight years ago, Dr. Haynes had been senior physician at the state hospital for the feeble minded at Faribault, Minn. He was born on the family homestead near LeGrande, Iowa. He graduated from the medical college of Drake University in Des Moines and practiced medicine for several years in Iowa before coming to the West River country of South Dakota.

* * *

dr. daniel v. moore, 73, died in Sioux City, Iowa, February 8, where he had practiced for 30 years. Previously he practiced in Yankton, S. D. During his lifetime, Dr. Moore had several close brushes with death. He was in San Francisco during the earthquake and also survived a Colorado train wreck. His most notable escape occurred at the time of the sinking of the Lusitania when he was one of the 734 survivors of the 3,700 persons aboard. Dr. Moore was a graduate of the medical school of Creighton University, Omaha, Neb., in 1905.

* * *

dr. herbert m. knudtson, died at Talihina, Okla., where he was chief medical director in the Indian service. A native of Hunter, N. D., he had been in the Indian service at Neah Bay and Nespelen, Wash., in Alaska, and at Lawton, Okla. Following service in World War II, he had been at Albuquerque, N. M., before going to Talihina six months ago.

* * *

dr. gilbert d. lofflier, 84, former Sioux Falls, S. D. physician died at his home in Lincoln, Neb., February 3. Before moving to Lincoln in recent years, Dr. Lofflier had also resided in Yankton, S. D.

* * *

dr. john e. countryman, 82, pioneer Grafton, N. D., physician died February 15 in Wheeler, Ore. He practiced in Grafton for 38 years, retiring in 1938 and moving at that time to Oregon. A former president of the North Dakota Medical association, and a member of the state medical examining board for several years, Dr. Countryman had received his medical degree at Queens University, Ont., Canada, in 1893.

SOME CURRENT CONCEPTS OF VIRUSES AND TUMORS

(Continued from page 89)

weeks old. In this connection I need hardly remind you of the infections of young mice via the milk with Bittner's breast carcinoma virus. Infection of mice by injection of this agent seems to lead to tumor production only if they are less than six weeks old.

To all these examples, with which you are probably already familiar, I can now add another, not yet published. My colleague, Dr. A. W. Gledhill, and I are now studying a hepatitis virus which has turned up in mice (Gledhill and Andrewes[16]). As with the many known pneumotropic and neurotropic mouse viruses, it is made manifest by serial blind passages. Thus liver or other organs of the Parkes strain of white mice are ground up and inoculated intraperitoneally to more mice preferably of the VS strain (Webster's bacterium-susceptible, virus-susceptible Rocefeller mice). After a week, suspensions of livers of these animals are similarly passed intraperitoneally to more mice, and so on. After two, three or more passages, inoculated mice begin to die with extensive liver lesions. The agent of this is readily shown to be a fairly large virus which will infect young VS mice in dilutions of 1 in 10,000 or more. The great interest of this agent to us is that it can be recovered not only from liver but from blood of normal Parkes mice, most of which seem to carry it. The VS mice do not carry it, and until they attain the weight of about 15 gm. are very susceptible to lethal infection. A hepatitis-producing virus in the blood of normal mice is naturally something of much interest to those studying serum-hepatitis in man. One hopes that our mouse virus may belong to the same family and give useful clues applicable to the human disease. I will add in parenthesis that aureomycin and terramycin are very effective against the mouse virus in prophylaxis but not therapy.

For our present argument, however, other aspects of the virus interest us. As soon as they are weaned, the Parkes mice are highly resistant to infection, while VS mice are quite susceptible. Experiment shows that this is an active, not a passive, immunity. What happens if we change at birth a Parkes and a VS litter? We find that the Parkes mice are still resistant, though we cannot yet say if they have acquired an immunizing infection before birth or within the few hours after birth before being removed from their latently infected mothers. Most of the VS mice fostered on Parkes mothers are also resistant and in this instance it is clear that an immunizing infection has been acquired after birth. In one of three attempts, virus has been obtained from the milk of the mothers. In the successful attempt, milk was obtained by killing the mother, opening her up, lightly scarifying the mammary glands and pipetting off the milk. Such milk was not completely free from blood, but virus was obtained after one blind passage from such milk diluted 1 in 10 and 1 in 100, while it was yielded rather less readily from a 1 per cent suspension of viscera. Further experiments to prove whether virus is transmitted wholly or partly in the milk are in progress.

Though these baby VS mice readily picked up infection while sucklings, we have as yet failed to show that weaned VS mice will acquire infection or immunity when caged along with infected animals. Possible analogues with the mammary tumor virus are obvious. What would be satisfactory to complete the analogy would be discovery of a way of activating the latent infection by dietetic or other insults in later life. This we shall attempt. I suspect that it may be possible, since before discovery of this virus I had met, not infrequently, with sporadic instances of fatal massive liver necrosis in adult Parkes mice. I never succeeded in revealing a viral or other cause for this; but of course I had not then the knowledge that newly weaned VS mice might be necessary to bring it to light.

In some experiments we crossed Parkes males with VS females and made other crosses in the opposite direction. Most litters were immune, whichever way the cross was made. We have yet to discover whether Parkes fathers infected VS females and they in turn infected their young, by milk or otherwise; or whether infection passed directly in the sperm or to the young after birth. These experiments will recall to you similar ones carried out by Dr. Andervont with the mammary tumor virus.

If the arguments I have been using are valid, we have to conceive of a cancer virus as one handed down from one generation to another either in the germ plasm or to very young animals, as an agent persisting indefinitely and producing no disease until activated, usually late in life, by appropriate stimuli. In the extreme case, the virus is conceived to be permanently in what I have called the vegetative phase, always passed by the hereditary mechanism, incapable of coming out and infecting new cells. The mouse cancers which Professor Bittner studies do not of course represent this extreme case, but other mouse tumors, in which no milk factor is demonstrable, may do so.

The tumors which are readily reproduced with filtrates, particularly those of fowls, may have done cancer research a great service and at the same time a great disservice. On the one hand they have drawn forcible attention to the fact that viruses can be the continuing cause of cancers, a truth ably expounded by Rous, Gye and others. On the other hand they may have led people falsely to expect that with a little better technical knowledge it might be possible to reproduce all kinds of tumors by means of filtrates. The agents of the filterable fowl sarcomata may be altogether exceptional in not having, like other tumor viruses, lost the power of going into the reproductive phase of the life cycle

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(Continued from page 112)

which allows direct infection of fresh hosts. It may be that there are viruses causing mammalian cancers which cannot be demonstrated because they are so extremely labile. I would be prepared, however, to hazard a guess that even if a virus is their continuing cause, most mammalian tumors will never be filterable as the Rous sarcoma is filterable. Three years ago Gye and his colleagues reported that a number of mouse tumors would survive freezing and drying and concluded that since intact cells could not be expected to survive such treatment, one had to conclude that transmission by a virus was established. Most people were reserved in their judgment, awaiting more evidence as to whether freezing and drying did necessarily kill all cells. Craigie's[17] subsequent work has shown clearly that while freezing and drying and even suspension in saline will kill most normal cells and most tumor cells, there is a particular state of the tumor cell which is quite unexpectedly tough. Cells in such a state, which he calls "paramorphic," can be readily recognized by phase contrast microscopy; they can resist freezing and other insults which destroy ordinary cells, but readily pass over to the ordinary condition and then regain their susceptibility to these insults. These findings show that particular evidence adduced in favor of the virus theory has not the weight ascribed to it; but all the facts are still consistent with the virus theory in the form in which I am trying to present it.

CONSIDERATION OF PARTICULAR TUMORS—FOWL SARCOMATA

Fowl tumor viruses of which the virulence has been enhanced by passage differ widely from the run of tumor viruses as I imagine them. But fowl tumors as they occur in nature are not so different from other tumors. They turn up sporadically like tumors of other creatures and are of assorted histological types; most of them are not at first filterable and all go through nonfilterable phases. If it were proven tomorrow that viruses had nothing to do with most cancers, we should still be faced with the anomaly of the sporadic occurrence in fowls of histologically varied tumors of which a virus could, with due care and labor, we shown to be the cause. It may be that with further work the discrepancy between the fowl sarcomata and other tumors will become less evident. Duran-Reynals[18] has published much interesting work in this field and I feel it would be worth while for others to make studies on similar lines. He observes that the Rous virus, when given intravenously to ducklings less than one day old, will produce either immediate tumors like the Rous sarcoma itself, or occasionally late tumors differing histologically and behaving like spontaneous duck tumors. Naturally occurring propagable duck tumors like these are not, however, on record. The possibility

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(Continued from page 113)

exists that these ducks acquired a latent infection with Rous virus, that this had time to vary and adapt itself to duck cells and that some carcinogenic stimulus in later life activated it. The importance of Duran-Reynals' work is its emphasis on the plasticity of tumor viruses; proof of such plasticity would help us to get away from the need to postulate a different virus for every kind of tumor.

SHOPE'S PAPILLOMA AND THE DERIVED CANCERS

I have already referred to Shope's papilloma and to the difficulty in serially transferring it in domestic rabbits. It may be that in this unnatural host, the virus is growing mainly in the vegetative form or at any rate failing to complete its developmental cycle. The cancers which so regularly derive from the domestic rabbit warts rarely have virus directly demonstrable in them. Kidd and Rous[19] could show that rabbits bearing transplanted cancers of this kind developed in their sera antibodies to the papilloma virus, evidence that virus was still there. But after further transplantations, even this evidence for presence of virus was lost. The natural tendency would be to argue that here was proof that the papilloma virus was merely a passenger in the transplanted cancers and not their continuing cause. But equally it may be that the virus has reached a state of closer integration with the cell, perhaps failing to elaborate, the antigen associated with the papilloma virus' infectiousness, and therefore no longer stimulating the rabbit to make the corresponding antibody. Kidd demonstrated the presence in these transplantable cancers of a complement-fixing antigen having the size and other properties to be expected of a virus but without any infectivity. He had previously demonstrated a similar but antigenically distinct entity in the nonfilterable Brown-Pearce carcinomas of rabbits (Kidd[20]).

MOUSE LEUKEMIA

Gross (1951)[21] has recently reported work on mouse leukemia which would fit in very prettily with the ideas we have been discussing. Just as Gledhill and I did with our hepatitis virus, and as Bittner has done with his mammary cancer virus, Gross worked with a strain of mice carrying the virus and with one which was free. Of his carrier strain, most developed leukemia late in life. Mice of the leukemia-free strain could be infected with the leukemia agent, and with filtrates of it, particularly if they were one day old or less. Baby mice so infected developed leukemia, not immediately, but on attaining middle age. This virus was not carried in the milk but was present in unborn embryos; extracts of these embryos, which would have grown up to be leukemic later on, also carried the infection when injected into day-old mice of the susceptible strain. One awaits with interest confirmation of this remarkable story which sounds like the mammary cancer virus story

(Continued on page 116)

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all over again with the difference that the mice are born with the agent in them and don't have to pick it up from their mothers' milk. And lest anyone should be thinking of these things as "agents" or "factors" or something other than a virus, let me once again point to our mouse hepatitis virus as an organism which knows just the same tricks to play.

Of the *mouse mammary cancer* virus it would be presumptuous of me to say more, since you know so much more about it than I do. I will mention in passing Lucké's[22] *leopard frogs* and their *kidney carcinomata* caused by a virus. The relevant point about them is that injection of tumor tissue into other frogs produces tumors late and in the kidneys rather than near the point of inoculation.

I have, I hope, made it abundantly clear how I suspect the relationship of viruses to tumors may be going to turn out. You may ask, "Well, suppose there are agents like the things you've been discussing, acting as the continuing causes of cancers; why are you so sure that they are extrinsic viruses and not bits of the cellular mechanism which have taken a wrong turning?" In the absence of certain knowledge, every man is entitled to his own guess. I find the notion of a cellular mechanism "gone berserk" something wholly speculative and unrelated to any solidly-based facts. On the other hand, there seems to be a continuous series from the viruses with the measles type of behavior through the latent infections to agents of which the direct transmissibility cannot yet be demonstrated. Of the theories in the field concerning cancer, the virus theory is still not a popular one, in fact a dark horse. All the same I know which horse I should feel inclined to back, and if I were a racing tipster, I'd be happy to put my friends on to a good thing. Too many of those who advocate, or condemn, the virus theory probably think of it as something very different from the picture I have tried to depict today.

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(Continued from page 98)

aggressive type of living brings about a state of continual anxiety closely related to nervous exhaustion and, at the same time, brings an increase in blood pressure. The man who is "always on his toes," always ready, a perfectionist, is a man who at the end of a day or a week will find himself exhausted.

The classic experiments of Walter B. Cannon, of Harvard, showed the remarkable increases in blood pressure which can be produced by anger, fear, and continual over-stimulation of the adrenals, and the habitual development of changes in the walls of the blood vessels. More than one individual has suffered a stroke or a pain in the heart and indeed a coronary occlusion from outbursts of anger, fear, or continual emotional over-stimulation.

The common symptoms of palpitation, a fulness in the head, dizziness, mild or severe headaches, light-headedness, vague pains in the chest, tingling in the fingers, or excessive perspiration may indicate the presence of a sharp increase in blood pressure.

The body type (mesomorph) and the nervous reactivity of an individual is an endowment from his parents. The man often shows the same pattern, build, and temperament as his father. His father may have died as the result of high blood pressure and the son may be a likely candidate. But, the father may have been subjected to long continued emotional overstrain and, in addition, have followed the practice of over-eating. Heredity by no means completely determines the quality of an individual's life and longevity. For example, the son of a father who has been overweight will do well to avoid the damaging effect of obesity. The son whose father was of an extremely nervous temperament will do well to take steps to live a more moderate, even-tempered existence. A great deal more is known today than in father's and grandfather's time concerning healthy modes of living and conduct.

Unfortunately, the tension of the times and the turbulence of family, community, and national existence works against even tempered, wholesome, living.

In my experience three out of four who show increase in blood pressure in the early stages of life may be readily controlled with little difficulty. Increased strain of the physical body, the nervous system, and long continued worries, lack of rest, lack of recreational periods may set the stage if neglected for the development of high blood pressure.

CLINICOPATHOLOGICAL CONFERENCE

(Continued from page 102)

tritis such as is seen in pernicious anemia. The spinal cord showed vacuolization in the dorsal and lateral columns. An incidental finding was a mild chronic thyroiditis with adequate remaining thyroid tissue. The hyperplastic bone marrow, atrophic gastritis and changes in the spinal cord are fairly good evidence for pernicious anemia.

DR. PAUL HAGEN: This case illustrates a danger of multivitamin capsules with folic acid. A recent article emphasized this point.[1] The authors described ten patients with pernicious anemia. Five had predominantly neurological changes and two had essentially normal blood values. In such patients the diagnosis of pernicious anemia would be easy to miss. Folic acid can be followed by just such a picture, i.e., neurological changes with nearly normal hematologic findings. Some of these multivitamin preparations contain vitamin B_{12}, but that does not mean they suffice for the therapy of pernicious anemia. The treatment of pernicious anemia is vitamin B_{12} given parenterally.

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Classified Advertisements

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FOREWORD . . . .

The editorial board of JOURNAL-LANCET has a gift for persuading competent authorities in carefully selected areas of tuberculosis work to contribute to this annual tuberculosis issue, so as to give a good cross section of problems and programs receiving current emphasis.

Tuberculosis workers throughout the country have become thoroughly aroused regarding the tuberculosis problem among Indians. Minnesota has been a pioneer in showing what can be accomplished through a sound program relentlessly and steadily applied. Senator Thye and Representative Judd are again sponsoring Federal legislation which most tuberculosis workers feel will be a a helpful step in the solution of this problem; namely, transferring the jurisdiction of the hospital and medical program of the Bureau of Indian Affairs to the United States Public Health Service. Dr. Leggett's paper therefore is of special current interest.

Minnesota has pioneered and still is pioneering in showing the role the tuberculin test will and should play in tuberculosis control programs. Few men have had more experience in this aspect than Dr. Sidney Slater of Worthington.

Having been most favorably impressed by Dr. Sumner S. Cohen's summary of isoniazid in the treatment of tuberculosis which he presented at the Mississippi Valley Tuberculosis Conference in St. Louis last fall, I am sure his paper will be most useful. Be prepared for as conservative expressions as you have ever encountered!

I am always interested in the report of the tuberculosis committee of the American College Health Association. And Ben Kuechle can write authoritatively on the insurance and workmen's compensation aspects of tuberculosis among all of the various groups of the population. Since no person is more important in the tuberculosis control program than the general practitioner, Dr. Meyer's article, therefore, is particularly timely.

I shall not comment on the rest of the contents, although equally intriguing, but close this introduction with congratulations to the JOURNAL-LANCET for another stimulating and important number devoted to tuberculosis.

JAMES E. PERKINS, M.D.,
Managing Director, National Tuberculosis Asociation

Pyricidin (Isoniazid) in the Treatment of Pulmonary Tuberculosis*

SUMNER S. COHEN, M.D.
Oak Terrace, Minnesota

THE DISCOVERY of antibacterial agents capable of inhibiting the growth of tubercle bacilli has led to tremendous advances in the treatment of pulmonary and other forms of tuberculosis. Streptomycin and para-aminosalicylic acid (PAS), given concomitantly, are potent anti-tuberculosis drugs. Streptomycin is given by intramuscular injection, usually one gram every third day or twice a week, while PAS is taken orally in doses of 10 to 12 grams daily, divided into three or four doses after meals.

Although streptomycin and PAS are effective when used together, certain patients develop toxic or allergic reactions to one or both drugs necessitating discontinuation of treatment. Bacterial resistance to streptomycin or PAS, while infrequent, does occur and at times the results of their use are not as complete as anticipated. The announcement of the development of isoniazid (isonicotinic acid hydrazide), therefore, was hailed with great enthusiasm.

However, the passage of time has indicated that many problems relating to the use of isoniazid have not been answered fully and further investigations to determine its place in the treatment of tuberculosis are necessary.

Concentrations of isoniazid as dilute as 0.1 mcg. per ml. have inhibited the growth of tubercle bacilli in vitro and have been effective in controlling tuberculosis in experimental animals.

Isoniazid has an important advantage over streptomycin in that it is effective when taken by mouth while streptomycin is given by injection. PAS may produce anorexia, nausea, vomiting or diarrhea while isoniazid is well tolerated by the gastrointestinal tract. It is reasonable in cost, is easily synthesized chemically and is in abundant supply.

Our investigationof isoniazid (Pyricidin†) was instituted in March, 1952. Since that time 105 patients have been treated with 200 mg. and 400 mg. of isoniazid daily in divided doses twelve hours apart. These patients were alternated between the two regimens without regard to body weight or general condition. This report, except for bacterial resistance, is concerned with 69 patients who have completed six months of therapy. Thirty-three of the 69 received 200 mg. daily while the remaining 36 were given 400 mg. daily.

Those selected for treatment with isoniazid had long standing chronic, advanced pulmonary tuberculosis and remained in need of further help in spite of having received all the standard forms of therapy including surgery whenever feasible and, in most cases, other chemotherapeutic agents.

This selected group of 69 patients had the following characteristics:

1. The pulmonary tuberculosis was classified as far advanced in 55 and moderately advanced in 14;
2. Cavities greater than 2 cm. in diameter were present in 41;
3. Thoracoplasty had been performed in 21 and had been combined with pulmonary resection in four;
4. Other chemotherapeutic agents, usually streptomycin, PAS or Tibione had been employed without complete success in 46 of the 69 patients.

TOXICITY

Mild reactions, usually of a temporary nature, were occasionally observed and consisted of headache, vertigo, hyperreflexia and constipation. These minor reactions did not require discontinuation of treatment.

Two patients (of 53) being treated with 200 mg. of isoniazid daily developed recurrent "drug fever" which necessitated permanent discontinuation of therapy.

One patient (of 52) who received 400 mg. daily developed recurrent urticaria and another in the same group complained of severe peripheral neuritis. It was necessary to stop treatment permanently in both of them.

SUMNER S. COHEN *is assistant medical director at Glen Lake Sanatorium, Oak Terrace, Minnesota. He is also an instructor of Nursing, University of Minnesota and a consultant on diseases of the chest, Mount Sinai Hospital, Minneapolis.*

*This study was made possible by a grant from the Lasdon Foundation.

†The pyricidin used in this study was supplied by the Nepera Chemical Company, Inc., Yonkers, New York.

Laboratory studies to detect toxicity to the hematopoietic, renal and hepatic systems were carried out at frequent intervals throughout the investigation. No evidence of any unfavorable reactions was demonstrated.

CLINICAL EFFECTIVENESS

This study was undertaken primarily to determine the toxicity of isoniazid in the dosages employed and to ascertain the rate of emergence of bacterial resistance. Favorable clinical results relating to conversions of sputum or gastric cultures and moderate or marked roentgenographic improvements were not anticipated.

Favorable subjective changes usually occur soon after treatment with isoniazid is instituted. Improvement in appetite, gain in weight, reduction of cough, decrease in quantity of expectoration and reduction of fever to normal can usually be anticipated. These effects become apparent somewhat more rapidly with isoniazid than with streptomycin-PAS.

Sputum or gastric cultures were converted from positive for tubercle bacilli to negative in 45.8 per cent of the patients following six months of therapy. These results are tabulated in table I. Favorable results were obtained generally within three months and little change occurred subsequently.

TABLE I

Conversion of Sputum or Gastric Cultures

Length of Treatment	Positive	Negative	No Report
Start	56 (96.5%)	2 (3.5%)	11
One Month	37	24	8
Two Months	29	30	10
Three Months	32	27	10
Four Months	32	30	7
Five Months	32	32	5
Six Months	32 (54.2%)	27 (45.8%)	10

Moderate or marked roentgenographic improvements were noted in 13 (18.8 per cent) of the patients after three months of therapy. Similar degrees of improvement were demonstrated in 23 (34.8 per cent) of the patients following six months of treatment. Favorable roentgenographic changes continued to increase throughout the six months of treatment in contrast to the conversions of sputum or gastric cultures which levelled off after three months of therapy. The degrees of roentgenographic changes in all cases are listed in table II.

BACTERIAL RESISTANCE

As noted in table III, increasing bacterial resistance can be demonstrated within three months of therapy and continues to increase with longer periods of treatment. Following six months of continuous treatment with isoniazid nearly all the patients exhibited increased organismal resistance and in 70 per cent of them it was considered more or less complete.

TABLE II

Roentgen Changes

	3 Months		6 Months	
No change	34		25	
Improvement				
slight	20		16	
moderate	10	18.8%	18	34.8%
marked	3		5	
Worsening				
slight	0		1	
moderate	2		0	
marked	0		1	
Unable interpret due resection	0		3	

TABLE III

Development of Bacterial Resistance

Length of Treatment	Number of Patients	Sensitive	Partially Resistant	Resistant
Start	74	72	1	1 (1.4%)
Three months	32	11	3	18 (56.2%)
Six months	20	2	4	14 (70.0%)

Tubercle bacilli were considered to have developed more or less complete resistance when appreciable growth was present in tubes containing 5 mcg. of isoniazid in one ml. of culture medium. If growth was absent in tubes containing 5 mcg. per ml. but was demonstrated in tubes with 1 mcg. per ml., the organisms were interpreted as being partially resistant.

It should be emphasized, however, that we do not know whether these levels of bacterial resistance are clinically significant and, so far, there is no definite evidence that they are. Past experiences with other chemotherapeutic agents would indicate that increasing bacterial resistance, demonstrated by laboratory methods, is important from the clinical standpoint.

COMMENT

Isoniazid appears to be a drug which is clinically effective, but its exact place in the treatment of pulmonary and other forms of tuberculosis has not as yet been determined. Streptomycin-PAS remains the standard form of chemotherapy in general use at the present time.

The greatest usefulness of isoniazid to date has

(Continued on page 152)

Results of Miniature Chest X-ray Program*

H. MILTON BERG, M.D., R. O. SAXVIK, M.D.
and KENNETH MOSSER

Bismarck, North Dakota

THE miniature chest survey program was placed in operation in North Dakota by the State Department of Health in April 1946. The late Dr. J. O. Arnson was chairman of the state committee on tuberculosis at that time. This program was approved by the State Medical Association upon recommendation of the Committee on Tuberculosis, with the following provisions: (1) all miniature films would be interpreted by the radiologists of the state, and (2) the patient who showed pathology on the miniature film would be referred to his private physician for examination and a 14 x 17 film.

These two provisions have made this one of the best programs in the United States. In many states the interpretation has been done by men not properly qualified. This has created a tremendous amount of confusion. In one state physicians complained of bizarre diagnoses that were received from the miniature chest program. I happen to know that at that time in that state the films were being interpreted by a technician.

The insistence of the committee that all required 14 x 17 films be taken by the doctors of the state, has kept the private physician and patient relationship intact. In many states arrangements were made for a unit to go back in the area and take all 14 x 17 films. This has tended towards a socialized medical type of program, which we have avoided.

Representatives of the United States Public Health Service in charge of the program for this area were most cooperative. Dr. Herman Hilleboe and Dr. Theodore F. Hilbish, two of the earlier men in charge, assisted us in many ways in setting up our program and saw to it that we received more than our share of federal financial help. Dr. Paul V. Joliet, who has been in charge of the USPHS program in this area for the past four years, has also been extremely cooperative.

The North Dakota Tuberculosis Association assumed the cost of all 14 x 17 films on patients unable to pay. They also contributed financially to the cost of the survey and assisted in every possible way to make this a successful project.

The aim has been to attempt to survey with miniature chest films one-third of the state area each year. This means that at the end of three years the unit will have covered the entire state and the fourth year will begin again in the area in which they started.

They have also attempted to cover completely every college each year. This college survey has been fruitful, in that we have picked up a few early cases among students every year. These potential sources of infection have been removed and placed under treatment much earlier than if they had been detected under normal circumstances.

It has also been our aim to include all the personnel of every large hospital in the state each year. In Bismarck, despite the utmost care in selecting workers, we have detected a case of tuberculosis among hospital personnel in almost each yearly survey.

Figure 1 is a sketch of the mechanical setup of the miniature chest unit. These units use a camera to photograph the fluoroscopic image of the chest. It requires a large amount of energy to energize the screen so that the fluoroscopic image will be bright enough to be photographed satisfactorily and the exposure time short enough to avoid movement. To fulfill these requirements, we have to work at a distance of 42 inches, tube-screen distance. The exposure is controlled by a photoelectric cell. The units carry their own power plant. Technic must be meticulous to obtain satisfactory films.

At the beginning of the survey program patients were required to undress, thus making the number who could be filmed per day quite low. USPHS studies have shown that few films would

H. MILTON BERG *is president, Rocky Mountain Radiological Society;* RUSSELL OLIVER SAXVIK *is professor of public health and preventive medicine, Medical School, University of North Dakota;* KENNETH MOSSER *is director of the Miniature Chest Program and has served effectively as liaison between the program and private physicians and radiologists.*

*Presented at the meeting of the North Dakota State Medical Association, Fargo, North Dakota, May 12, 1952.

be unsatisfactory for survey purposes if the films were made without the patient undressing. However, the subject is requested to remove outer clothing, empty pockets and women are requested to remove breast pins and necklaces before the film is taken. We adopted this method of filming early in the program and are able to film up to 60 patients per hour. An unsatisfactory film because of clothing is rare.

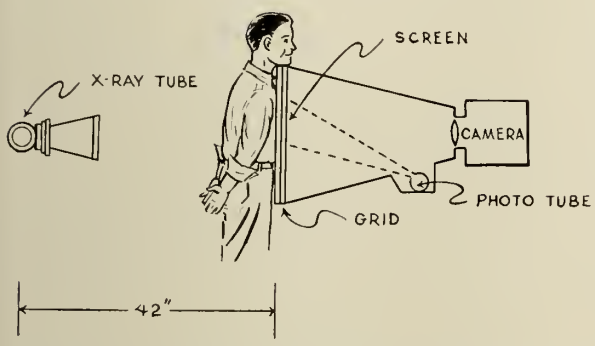

Fig. 1. This sketch shows the arrangement for taking miniature chest x-ray films. The tube-screen distance is 42 inches. A stationary grid is used in front of the fluoroscopic screen to reduce secondary radiation and give sharper films. The broken lines from the photo tube show the area scanned by the tube to control the exposure time.

Due to the 42 inch tube-screen distance, the program is of no value in detection of early cardiac enlargement. The heart at this distance is magnified in relationship to the size of the chest. However, we are able to detect any change in configuration and any marked change in size.

Small early pulmonary lesions show up almost as well on the miniature films as on the large films. We have had the opportunity to compare a large number of cases in which we had both the miniature and the large film available, and it is remarkable how well small lesions show up on the miniature film.

The films have all been read by North Dakota radiologists. We had to develop a rapid method of reporting and adopted the following type of card for the report.

All patients are referred to the physician whom they select. If one states that he has never been to a doctor he is asked to whom he would go if he were ill and this name is used. If the patient refuses to select a physician, the district or county health officer for that county is listed as the physician who is to receive the report of the miniature film.

The first item on the card is "negative." The films are marked negative if no cardiac pathology appears to be present and the lung fields appear clear. We ignore rib abnormalities and any other changes which are of no significance.

The second is "unsatisfactory." An unsatisfactory film can be due to the patient breathing or moving during the exposure. The technician watches carefully and if the patient appears to have moved or breathed he retakes the film. An unsatisfactory film may also be due to mechanical difficulties, such as the rough roads over which equipment is moved. In one county the camera lens had rotated due to rough roads and as a result all films were out of focus. The photo-electric cell may stop working properly and give us incorrect exposures. One of the relays may stop functioning and give unsatisfactory films. In one survey the manufacturer sent the wrong type of film which was not noticed

PHOTO-FLUOROGRAPHIC FINDINGS

1. Negative ☐
2. Unsatisfactory ☐
3. Tuberculosis Pathology ☐
4. Suspicious Tuberculosis Pathology ☐
5. Other Pathology: Cardiac, Tumors, Etc. ☐
6. Remarks, Recommendations, Re-examine for ☐

(Radiologist) (Address)

Project No. Date Taken

PLEASE PRINT OR TYPE

Number

Name
(Surname) (First) (Middle)

Age. Sex. Race.

Marital Status: Married Single.

Husband's

Address
(Street) (City)

Family Physician

Physician's Address

(A)
(Location Preferred)

(B)
(Time Preferred)

until over 200 exposures had been made. This film had a different speed and none of the exposures were satisfactory.

As the program has developed, excellently trained technical help has been obtained. Therefore, our unsatisfactory films are now a little over 2 per cent.

The third item on the card is "tuberculosis." Strictly speaking no radiologist has the right to state that any lesion is definitely tuberculosis. However, films that from a radiologist's point of view appear to be probable cases of active tuberculosis are given this diagnosis. Some of these cases may later be found to be carcinoma or some other disease.

The fourth classification is "suspicious for tuberculosis." Films that show changes which could be a tuberculous process are given this diagnosis. Many of this group will be found to be fibrosis from an old tuberculous process which is stabilized. A considerable number of cases, after study by the family physician and the taking of large films, will be found to have no active pulmonary pathology. A fair proportion has been proved to have active pulmonary tuberculosis.

Groups five and six are used for non-tuberculous conditions such as enlarged heart, substernal thyroid, lung tumors and other miscellaneous conditions. In these two classifications we write out our diagnosis on the card. We are now setting up a new group for chest tumors which will be number 7. This will make it easier to follow these cases in the future.

In the survey we try to avoid taking films of people who are under treatment for tuberculosis as well as those who have had chest surgery. We do not feel that we would know enough about the case to make a satisfactory interpretation from the miniature film. Despite careful screening, some of these types of cases slip through and are taken. When this occurs we report them as unsatisfactory for survey studies.

We also try to avoid taking children under 15 years of age, except when the survey is in a high school where we are taking everybody in the school. The incidence of pulmonary tuberculosis in children under 15, under average conditions, is low. Most miniature chest surveys omit them, since the number of cases of pathology detected are too few to justify the expense. However, if the survey were to be made of an Indian reservation, children should be included.

The miniature film can be read in three ways:

1. Interpret the film with idea of picking up only gross pathology.
2. Read film more carefully and report a greater proportion of the changes that may represent pathology.
3. Overread the films and report even minimal changes as possible pathology.

The only way not to miss the cases of early tuberculosis and early lung tumors, which are the cases that would derive the greatest benefit from early detection and treatment is to overread the films. In overreading all minimal changes are reported as suspicious. When one reads films in this manner it means that a large number will be referred to the family physician for study and a good proportion of these cases will eventually have a diagnosis of no disease.

We overread the films the first three years, and I think we missed very few cases. We then began to have some complaints from the physicians that they were being referred too many cases that turned out to be negative. In 1949 and 1950 we did not read the films as closely, with the result that fewer patients were referred to their doctor for further study. During this two-year period, later follow-up studies indicated that we had missed a few cases of early pulmonary tuberculosis. In 1951 we again started overreading the films and we have lowered our incidence of missed cases.

There is no absolute way to determine how many cases we have missed. Our only method of follow-up is the case in which the doctor advises us that he has a patient with pulmonary tuberculosis who had a negative report on the miniature film. The North Dakota State Tuberculosis Sanatorium at San Haven also advises us whenever a patient is admitted who has had a miniature film with a negative report. All of these miniature films have been reviewed. In some instances the miniature film was negative at the time it was taken, which may have been some months or even years before the diagnosis of tuberculosis was made. Once or twice each year a case is reported in which, upon receiving the miniature film, we find we missed a tuberculous process and gave a negative report. In some of these cases the lesion was underneath a rib. One must always keep in mind that 25 per cent of the lung field is obscured by ribs and heart.

The survey has been of value not only in detecting tuberculosis but also in detecting a large number of chest tumors, substernal thyroids, bronchiectasis, paraesophageal hernias, cardiac pathology, and carcinoma of the lung.

N. DAK. STATE DEPT. OF HEALTH — Mass Radiography Form No. . . .
Div. of Preventable Diseases — NOTIFICATION REPORT

REPORT OF X-RAY EXAMINATION

On the date shown below an x-ray was taken of your chest. You will be glad to know that the condition of your chest appears satisfactory on the x-ray film.

However, even a person who is strong and healthy today could have a condition a year from now. That is why we recommend that everyone over 15 years old have a chest x-ray every year.

This card is very valuable to you and the results of the examination should be kept for future reference. We appreciate your interest in keeping your community healthy.

Project Number . . . . Film Number . . . . Date Taken

As soon as these films have been reported the cards are sent to the Health Department. On the cases that are reported as negative, a card like this sample is mailed to the patient.

No report on the negative cases is mailed to the doctor as it is felt that it is not worth while to send the family physician a large number of negative reports.

The miniature x-ray of your chest that was made . . . . was unsatisfactory due to technical difficulties, therefore:

WE SUGGEST YOU HAVE A RETAKE AS SOON AS POSSIBLE.

Watch the local newspaper for the dates when the Unit will be in the area near your residence.

R. O. SAXVIK, M.D.,
State Health Officer

In the cases which are reported as unsatisfactory, the patient is the only one notified and is sent this notice.

NORTH DAKOTA STATE DEPARTMENT OF HEALTH
BISMARCK

DIVISION OF PREVENTABLE DISEASES

We have notified your family physician . . . . that a miniature x-ray made of your chest on . . . . by the Mobile X-ray Unit shows findings which may be suspicious of a disease.

An examination by your family physician is necessary. If he advises a 14 x 17 chest x-ray and you feel you cannot afford it, consult your county health nurse or county superintendent of schools. They can give you an authorization for an x-ray film to be paid for by the Christmas Seal Fund of the Tuberculosis Association.

The authorization is for payment of one 14 x 17 x-ray only. Payment for physical examination and additional x-rays is the responsibility of the patient.

We suggest that you see your doctor at once.

Sincerely yours,

R. O. SAXVIK, M.D.,
State Health Officer

Survey Film No. . . . . .
Mobile Unit Letter No. 2

If the report is "tuberculosis" or "suspicious for tuberculosis" this letter is sent to the patient. It stresses that an examination by his family physician is necessary and that he should see his doctor at once.

In cases in which the diagnosis is "tuberculosis" or "suspicious for tuberculosis," a letter is sent to the physician listed by the patient.

Space has been provided on the bottom of the letter so that the doctor can report his findings to the health department with very little effort.

If the patient fails to come in to see the doctor within three weeks, the doctor should return the blank and check that the patient did not report.

In all localities with public health nurses, which is 39 of the 53 counties, the nurse is notified of all the cases reported as having tuberculosis or being suspicious for tuberculosis. If within 30 days after the doctor is notified of these findings, the nurse has not received a report that the patient has reported to his physician, she tries to contact him and urge him to report. Due to the heavy load of most of the public health nurses, some time may elapse before she is able to contact the patient.

The average patient reports to his doctor shortly after receiving the letter from the Health Department. As soon as the doctor has had the opportunity to examine the patient and have a large chest film made, he should write his diagnosis on the bottom of this letter and return the completed form to the Health Department.

Cases which are reported as a large heart, possible tumor and other nontuberculous conditions, a notifying letter is sent to the patient and another letter is sent to the doctor with the diagnosis made by the radiologist from the miniature film.

TABLE I

SUMMARY OF MOBILE SURVEY

Five Year Period 1947 to 1951 Inclusive

	1947	1948	1949	1950	1951	Total
Total satisfactory films	89,591	70,246	56,820	71,143	72,806	389,660
Negative	85,435	67,839	55,379	69,433	69,683	374,767
Suspicious for tuberculosis	1,966	1,361	868	586	2,250	7,031
Tuberculosis	117	116	36	23	40	332
Other pathology	2,073	930	537	1,101	833	5,474
Referred to physician	4,156	2,407	1,441	1,710	3,123	14,893

The Health Department is going to try to follow-up all cases of possible chest tumors this year so that we can have an accurate determination of the value of this survey as far as detecting chest tumors is concerned.

Table I shows the operation results of the survey for the past five years. Note that in this five-year period we had 332 cases that the radiologist thought had definite active pulmonary tuberculosis and that 7,031 cases were suspicious for tuberculosis.

In 1950 and 1951 the Health Department tabulated the replies from the physicians as to the diagnoses on the cases referred to them, with a diagnosis of pathology from the miniature film. A final report was received from the physicians in 3,121 cases out of 4,833 referred to them. The results are shown in table II.

TABLE II

RESULTS MOBILE UNIT SURVEY 1950-1951

Total x-rays	147,524
Total number referred to physician with diagnosis of pathology	4,833
Report received from physician	3,121
(Statistics below based on this number)	
Essentially negative	1,004
Individuals refusing follow-up	50
Healed primary tuberculosis	610
Patients with tuberculosis known previous to miniature survey	59
Inactive tuberculosis not on record	157
Active tuberculosis	81
Cases that are probably tuberculosis but require further study to determine activity	84
Diagnosis reserved (patient had chest pathology but physician had not arrived at diagnosis at time of report)	131
Cardiac pathology	414
Pneumonia	38
Lung tumors	26
Substernal thyroid	37
Bronchiectasis	49
Hodgkin's disease	2
Other pathology	378

We reviewed all of the cases for 1951 in which we had made a diagnosis of pathology from the miniature films and tabulated the results which are shown in table III.

It is interesting that during 1951 there were 363 cases which appeared to have pulmonary or mediastinal tumor. There were 2,250 cases suspicious for tuberculosis and 40 that appeared to have definite active pulmonary tuberculosis.

TABLE III

TABULATION OF POSITIVE FINDINGS ON MINIATURE FILMS IN 1951 IN WHICH 72,806 FILMS WERE TAKEN

Suspicious for tuberculosis	2,250	Paraesophageal hernia	7
Tuberculosis	40	Possible histoplasmosis	11
Tumor	363	Pleural effusion	37
Enlarged heart	155	Pneumonia	16
Substernal thyroid	76	Bronchiectasis	7
Dextro-cardia	12	Miscellaneous	48

The program was started with the purpose of detecting cases of tuberculosis, and in this the survey has been very successful. This study, I believe, conclusively demonstrates that the survey has been just as valuable in detecting other pathology in the chest, such as cardiac pathology, and chest tumors.

One chest surgeon connected with the University of Minnesota, informs us that he has had five resectable carcinomas of the lung, and 12 cases of benign tumors of the lung, all of which required surgery, referred to him. These cases had been discovered by our miniature chest film survey. Another chest surgeon in Minneapolis with whom we visited recently, stated that he had operated on a large number of patients with benign lung tumors, and could recall at least six resectable carcinomas of the lung from this state. All of these cases had been detected by the miniature chest program.

When one multiplies the experience of these two men by the number of chest surgeons in the northwest, it demonstrates conclusively that the program has been very valuable in early detection of chest tumors, carcinoma of the lung, and many chest conditions besides tuberculosis.

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The Out-patient Service for Tuberculous Indians in Minnesota

ELIZABETH A. LEGGETT, M.D.*
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For many years the State of Minnesota has been concerned about the problem of tuberculosis among the Indian population. In October 1923, Chippewa health nurses were employed to work among their people. In 1924 a tuberculosis sanatorium for Indians was opened in an unused school building at Onigum. When the building burned in December 1934 the patients were carried across the ice to the Minnesota State Sanatorium at Ah-gwah-ching, and were cared for there in temporary quarters until August 1935, when the Chippewa Wing now known as the "E" Building was opened. This wing was built with federal funds to provide beds for the Indian patients. The per diem expenses of the Indian patients in the Minnesota State Sanatorium and in other sanatoria in the state are paid by the Indian Service under a special contract between the Federal Government and the State of Minnesota. Additional funds are provided for the surgical treatment of tuberculosis in those cases in which it is considered advisable.

The incidence of tuberculosis is much higher among the Indian than among the non-Indian population. In 1941 during a special tuberculosis survey conducted in Minnesota by the State Board of Health, the Chippewa Nursing Service, the State Tuberculosis Sanatorium Staff and the Indian Bureau Physicians, 229 cases of reinfection type tuberculosis were found among 4,670 persons examined. This represents a case incidence of 47 per 1,000. The diagnosis in many of these cases was based on clinical and laboratory examination only. It is felt that if all could have been x-rayed the incidence of diagnosed disease would have been even higher. Even after diagnosis has been established it is frequently difficult to convince the patient that sanatorium care is necessary. After admission to the sanatorium many patients leave against advice long before their disease is under control.

In 1950, after many months of planning, the Indian Out-Patient Service of the Minnesota State Sanatorium was started. It was planned as a diagnostic and educational service. Through it we hoped to secure earlier diagnosis of the disease: by physical and x-ray examination of the patients at chest clinics held at the Cass Lake, Red Lake and White Earth Indian Hospitals; by tuberculosis surveys in the schools with laboratory study including gastric cultures of those suspected of having active disease; by the checking of contacts both of patients with clinical disease and of those children found to have tuberculin reactions, particularly of those who were known to have converted to reactors. In addition to serving as diagnostic centers the clinics were to be used in the follow-up of patients discharged from the sanatorium. It was hoped through the follow-up service to make possible an earlier discharge of the patient from the sanatorium. Arrangements were made to continue pneumothorax and pneumoperitoneum treatments if indicated. However, about the time the service was started the general trend away from collapse therapy had started and we have not found the need to continue such treatment outside of the sanatorium. At the time of establishing the Out-Patient Service the policy of taking at least one 14 x 17 chest x-ray film on all patients admitted to the Indian Hospitals was initiated. The x-ray films are interpreted as part of the service rendered by the Out-Patient Department. Chest x-ray films are also taken on patients examined at the general medical clinic, if they show signs or symptoms of pulmonary disease.

Special funds obtained in 1950 for control of tuberculosis among the Indians of Minnesota were used in part to set up the Out-Patient Service and in part were invested in permanent equipment to be used in the diagnosis of tuberculosis. X-ray machines (300 milliampere) with special diagnostic equipment were installed in the Cass Lake and White Earth Hospitals, re-

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placing the 15 milliampere machines formerly used. A trained technician took charge of the laboratory at Cass Lake and served as technical consultant for the White Earth Hospital. The x-ray equipment at the Red Lake Hospital was deemed adequate. It is, however, hoped that in the future it may be replaced by a more modern machine. There is an opening for a technician at the Red Lake Hospital but so far no one has been found to fill the place.

The Out-Patient Service started work in April 1950 with a staff consisting of: a clinician, a member of the medical staff at the state sanatorium who conducted monthly clinics at the three Indian Hospitals, who interpreted x-ray films, who supervised the work of the service and at the same time continued a full-time service at the sanatorium; a full-time public health nurse who also served as coordinator. She assisted the public health nurse at the hospital in arranging for the clinics, in the notification of the patients, in the necessary home calls in tracing contacts, in the compilation of information concerning the patient, the personal and family history, the compilation of laboratory data. She arranged appointments for x-ray film examination, for laboratory tests and for future visits to the clinic. She made sure the required information was sent to the State Board of Health, to the State Nursing Office and to the Indian Hospital. She assisted the doctor at the clinics and helped in the preparation for the Mantoux surveys in the schools. Another important member of the team was the secretary, who started out on a part-time basis but whose services were soon required full time. She transcribed all records, filed them and sent copies to those designated to receive them. She recorded and filed the laboratory data and the results of the Mantoux tests. She handled the correspondence for the department.

In conducting the work of the Out-Patient Service close cooperation and coordination between the Indian Hospitals and their staffs of doctors and nurses, the Indian Service Public Health nurses, the Minnesota Public Health Nurses, the Minnesota Public Health Department, the State Sanatorium Staff, the Minnesota State Division of Social Welfare and the Area Office of the Indian Service are required. We have been fortunate in the excellent service each of these numerous divisions has supplied. The Indian Hospitals provide the space and the facilities for the clinics, they take and develop the x-ray films, obtain the gastric cultures requested, furnish transportation for the patient, assist the clinician in every way possible, and with great patience and forbearance allow us to disturb their usual arrangements and routine. They aid us with their detailed medical and personal knowledge of the patient. We greatly appreciate their willing and cheerful cooperation and have enjoyed the personal contacts formed with them.

We have found the public health nurses have played an important part in the success of the program. Their knowledge of each patient's family background, personal history and environment has been invaluable. Their skill and tact in handling the patients has made our work easy. The nurses have made the clinic appointments for the patient, have used their personal influence to see the appointments are kept, have driven endless miles over extremely bad roads to bring patients from their homes and camps to the clinic and then have made the same weary drive to return them to their homes. They have assisted at clinics: introducing patients, helping them dress and undress, supplementing their histories and, in turn, explaining and clarifying the physician's instructions to the patient. If for any reason the public health nurse has been away for a long period of time the number of patients reporting to clinic has decreased and fewer have responded to requests for x-ray films or other laboratory tests. One large district at the present time has no public health nurse. The patients reporting to clinic from this district are conspicuous by their absence. We are attempting to remedy this by establishing a clinic in the district itself. In the meantime we hope that a nurse will soon be obtained. We realize what heavy demands we have made on the time and strength of the nurses.

The first chest clinic was held at Red Lake on April 5, 1950, when 15 were examined. Three were found to have suspected reinfection type tuberculosis and their admission to the sanatorium for further study and treatment was advised. Since this start monthly clinics have been held at the Indian Hospitals at Red Lake, Cass Lake and White Earth. The number of patients seen at clinics varied from four to 28. The number examined at each hospital from April through December 1950 was as follows: Cass Lake 81, Red Lake 79, White Earth 89 (total 377). During the same time 1335 x-ray films were read. In 1951, 229 were examined at Cass Lake, 265 at Red Lake and 199 at White Earth and 3224 x-ray films were read. In 1952, 190 patients were examined at Cass Lake, 207 at Red Lake and 130 at White Earth and 3852 x-ray films were read. Since April 1952 the Ponsford district has

had no public health nurse. This has been reflected in the decrease in clinic patients from this district at the White Earth clinic. There is also a seasonal variation in the clinic attendance. In September and October Minnesota Indians are picking potatoes in Dakota.

The routine of the clinics is as follows: approximately two weeks before clinic the necessary x-ray films are scheduled to be taken. If possible they are read before the clinic. In preparation for the clinic, previous records and x-ray films are withdrawn from the files and are presented with the patient at the time of the clinic. An interval history is taken and the findings of the x-ray films, laboratory and physical examination are discussed with him. The future course is outlined. If clinical disease is found or suspected the patient is frankly told of the findings. If hospitalization is indicated it, also, is discussed. The usual procedure of admission, the usual course of treatment including chemotherapy as indicated, some rough estimate of the period of treatment is given. Possible arrangements for the care of the family are talked over and, if feasible, contact is made with the social service or welfare department. If possible, a definite time is set for the patient to come into the sanatorium. Patients who need further study are given appointments for future visits to the clinic. Findings suggestive of nontuberculous chest disease are discussed with the medical officer at the hospital. Authorization blanks for admission are signed by the patient or his parents and by the doctor, and started on their round. The clinics are also used as means of educating the patients and their relatives concerning the spread of tuberculosis and the precautions to take against it. Relatives of sanatorium patients attend clinics to obtain information concerning the present condition and the progress of the patients. They also pass on family news to be given later to the patient.

Those who have been discharged from the sanatorium report to the clinic for routine x-ray film and check-up examinations. Sputum tests, gastric cultures and other examinations are ordered as indicated and are obtained through the cooperation of the hospital and the State Board of Health laboratories. It has been interesting to see how many report for their check-ups. Practically all who leave with consent are most faithful in reporting. But those who leave against advice also come in to be examined. For instance, at Cass Lake, of the 12 who left against advice six have reported to clinic, two are in jail and cannot report, one went to Minneapolis and was returned to the sanatorium from there, and one other returned voluntarily to the sanatorium, two others who left shortly before they were to come up for discharge have failed to report.

In November 1952 the clinician was relieved of her duties in the sanatorium and has spent full time on the Out-Patient Service. Since then monthly clinics have been established at Naytahwaush, Ponsford, Bena and Inger. A clinic has been planned for Ponemah. We hope to have it in operation in April. When clinics are held in these outlying spots the 15 milliampere portable x-ray machine is taken along and the indicated x-ray films are taken following the clinic. They do not compare with those taken on the 300 milliampere machine but they are not too bad. The big problem is to find a room that can be used as a darkroom in which to change the films. So far these local clinics have been well attended.

We have also been able to give more assistance in the Mantoux surveys than before. When Mantoux surveys are held in isolated schools we bring the portable machine along and make x-ray films of reactors the same day the tests are read. If possible, the reports and the x-ray films are back to the school within a week.

The Indian Service has recently inaugurated the practice of inoculating all new-born infants with BCG. We hope to be able to follow these children and their older uninoculated brothers and sisters at clinic. In a few years time we should have information concerning the incidence of reinfection type tuberculosis in the two groups. The routine hospital admission x-ray films should help in following the uninoculated children. In about six years the school surveys will help too.

Of the new cases of tuberculosis admitted to the Minnesota State Sanatorium in 1952, eight were of active primary phase disease which were diagnosed on the basis of out-patient x-ray films and examination with positive gastric cultures which were taken at the request of the clinic, two were diagnosed on the basis of Mantoux tests, x-ray films and gastric cultures obtained while the patient was under treatment at the hospital. One case of miliary tuberculosis was diagnosed after admission to the hospital for treatment of "pneumonia." Three with minimal active reinfection type tuberculosis were diagnosed at clinic, one was diagnosed in the hospital and one was admitted on the basis of a mobile unit x-ray film. The last patient proved

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The Value of Tuberculin Skin Testing as a Case-Finding Procedure

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and DUANE STERNITZKY

ALTHOUGH the value of tuberculin skin testing as an educational medium is widely recognized, the value of the test as a case-finding procedure is not as widely accepted.

A tuberculin skin testing and x-ray survey, conducted among school children, teachers, and other school employees in New Jersey, from 1939 to 1949, uncovered 595 cases of reinfection tuberculosis among children of high school age.[1] Over 1,200,000 tests were given in the ten-year period.

In Chicago, a tuberculin skin testing survey has been reported upon among school children over a three-year period. By March 1, 1940, 167,345 individuals had been tested.[2] Two hundred eighteen cases of reinfection type tuberculosis and 4,524 cases showing evidence of primary infection were uncovered.

In view of Wisconsin's lower tuberculosis death rate, and the more rural characteristics of the state, the discovery of fewer cases of tuberculosis through skin testing of school children might be expected. The medical department of the Wisconsin Anti-Tuberculosis Association has made a survey of findings in tuberculin skin testing programs reported to have been conducted by Wisconsin public health nursing services in 1950. The year 1950 was chosen as the most recent year for which complete diagnosis and followup information would be available.

A questionnaire was designed to obtain (1) the number tested and number of reactors by major age groups; (2) active cases of tuberculosis discovered, with age of individual, classification of disease, and place cared for; (3) cases found among associates of reactors, with age of individual, classification of disease, and place cared for; (4) cases found through tuberculin testing in 1948, 1949, 1951, 1952; and (5) type of test given.

The questionnaire was sent to 65 nursing departments that had reported carrying on a tuberculin skin testing program in 1950. Sixty-four departments responded. Fifteen of these 64 replies were excluded from the tabulations for various reasons, such as unavailability of records, too limited a group tested, or that the program was initiated in a year other than 1950.

FINDINGS

The 49 remaining nursing services conducted 45,804 tuberculin skin tests in 1950. It is believed that this total includes approximately three-fourths of all tuberculin testing carried on in the state during the year.

TABLE I

CASES OF ACTIVE TUBERCULOSIS* FOUND AMONG REACTORS TO TUBERCULIN SKIN TESTING PROGRAMS, 1950, IN THIRTEEN WISCONSIN NURSING SERVICES

Age Group	*Total*	*Classification of Disease*			
		Primary	*Minimal*	*Mod. Adv.*	*Far Adv.*
TOTAL	22	8	6	5	3
1 to 5	4	4	–	–	–
6 to 12	4	4	–	–	–
13 to 18	10	–	6	4	–
Over 18	4	–	–	1	3

*Active primary tuberculosis may or may not be demonstrable. Symptoms may be absent, or are few or mild. There are usually no detectable abnormal physical findings. A reaction to tuberculin must be present. Roentgen film findings may not be noted. Less than one out of four reactors show abnormal x-ray shadows.

Of course, when suspicious shadows suggesting an x-ray lesion, either parenchymal or in the lymph nodes, are noted, and the young person has tubercle bacilli found through culture or guinea pig inoculation of material obtained from a fasting stomach, the diagnosis is definite. However, even when tubercle bacilli are demonstrated, the patient may still be asymptomatic. Sometimes a slight fever 99.5° to 100° F. is noted. Occasionally the "changed nature" child complex is manifested. The amount and type of x-ray change varies from time to time. Resolution of the first pulmonary or root shadows may occur or may be replaced in due time by fibrosis or calcium deposits or the lesions may progress into definite pulmonary disease. (*Diagnostic Standards*, 1950, published by the National Tuberculosis Association, and prepared by a series of committees of the American Trudeau Society, Medical Section of the National Tuberculosis Association, has an excellent discussion on primary tuberculosis, pages 13-17.)

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CASES DISCOVERED

Thirty-six nursing departments reported that no cases of active tuberculosis were found among reactors to the 1950 tuberculin testing programs. Thirteen nursing services reported a total of 22 new cases of active tuberculosis uncovered by the 1950 tuberculin skin testing programs. The age and classification of disease of these cases are given in table 1.

Twenty of the 22 cases subsequently entered sanatoriums. (Two primary active cases were cared for at home.) There were 18 active cases of tuberculosis found in the 18 years of age and under group. Slightly over 36,000 individuals in this age group were tuberculin tested. Hence, one active case was discovered out of slightly over 2,000 individuals tested. In addition to these 22 new tuberculosis cases discovered among reactors to the skin test, 7 associates of reactors were found to have tuberculosis in an active stage.

Three of the four departments reporting cases among the associates of reactors (see table II) had already reported cases among reactors; one had not. With the exception of the one primary case, all of the cases found among associates of reactors were admitted to sanatoriums.

TABLE II

ACTIVE TUBERCULOSIS CASES FOUND AMONG ASSOCIATES OF REACTORS TO 1950 TUBERCULIN SKIN TEST, FOUR NURSING SERVICES REPORTING

Age Group	*Total*	*Classification of Disease*			
		Primary	*Minimal*	*Mod. Adv.*	*Far Adv.*
TOTAL	7	1	2	–	4
1 to 5	1	1	–	–	–
6 to 12	1	–	1	–	–
13 to 18	1	–	–	–	1
Over 18	4	–	1	–	3

The completeness of followup examinations and reports of such examinations among associates of reactors is unknown. Hence the seven reported cases cannot be taken as an accurate measure of the incidence of tuberculosis among these associates. Subsequent investigation indicates that four and possibly six additional contacts of the original 22 cases discovered were admitted to sanatoriums after the 1950 testing programs.

The survey is weighted somewhat by the inclusion of one atypical community. This community tuberculin tested 464 Indians, of whom 138 were adults. Three of the cases among reactors (two were adults, diagnosed far advanced, one was a teenager diagnosed as minimal) and two of the cases among associates of reactors (the primary case, and an adult diagnosed far advanced) were discovered in this group. In general, however, the services included in the survey are representative of the state, with all sections of the state included except Wisconsin's one large city, Milwaukee.

Sixteen additional cases were found through tuberculin testing in the years 1948-49 and 1951-52. This was an incidental question, and the information is not being evaluated. No indication of the scope of the test in those years was included.

Other cases of active tuberculosis were listed by the nurses in several responses. These were not included in the tabulations as no tuberculin skin test was indicated.

REACTORS

The nursing departments' responses in respect to reaction are divided into two groups. The first group includes those 29 responses that report no active cases of tuberculosis found through tuberculin testing. The second group is composed of the 20 services that reported cases among reactors or associates of reactors during the past five years. Responses covering 37,122 tests, or over 80 per cent of those tested, indicated the type of test given. Ninety-six per cent of these 37,122 were tested by the intracutaneous test method, the remaining 4 per cent by the patch test method.

DISCUSSION AND SUMMARY

Forty-nine nursing services in Wisconsin reported 45,804 individuals tuberculin skin tested in 1950. Somewhat over 36,000 of these individuals were known to be under 19, and 18 cases of active tuberculosis were discovered among them. These 36,000 persons, however, comprise less than 4 per cent of the "under 19" population of the state. If those tested were representative of the entire state—and it is felt, by and large, they were—over *250 new* cases of active reinfection tuberculosis and over *200 new* primary active tuberculosis cases would be uncovered if the entire "under 19" group of the state were tuberculin tested and reactors x-rayed.

Seven, and possibly 13, cases of active tuberculosis were uncovered among associates of reactors to the test. Since followup work is often done by some agency other than the nursing service conducting the test, there may have been other cases uncovered in the programs which are unknown to the writers.

TABLE III

NUMBER OF TUBERCULIN TESTS, NUMBER OF REACTORS, AND PERCENTAGE OF REACTORS, IN 49 WISCONSIN NURSING SERVICES THROUGH TUBERCULIN TESTING PROGRAMS, 1950

Age Group	49 *nursing services answering questionnaire*			29 *nursing services reporting no active cases found by tuberculin testing*			20 *nursing services reporting active cases of tuberculosis through skin testing programs in 5 years* – 1948-52		
	Number		*Percentage of reactors*	*Number*		*Percentage of reactors*	*Number*		*Percentage of reactors*
	Tested	*Reactors*		*Tested*	*Reactors*		*Tested*	*Reactors*	
TOTAL	45,804*	2,525	5.9	20,629*	687	3.8	25,175	1,838	7.3
1 to 5	567	11	1.9	491	4	.8	76	7	9.2
6 to 12	9,122	437	4.8	3,853	90	2.3	5,269	347	6.6
13 to 18	18,216	1,057	5.8	8,612	370	4.3	9.604	687	7.2
School children – age not specified	8,317	281	3.4	4,522	108	2.4	3,795	173	4.6
Over 18	1,710	413	24.2	467	109	23.3	1,243	304	24.5
Age unknown	5,227	328	6.2	39	6	15.4	5,188	320	6.2

*Includes 2,645 who were tested, but on whom the reaction and age classification are unavailable.

The progression of the disease was less advanced in the cases discovered through tuberculin testing, than in the average sanatorium admissions. Only three of the cases found among the tuberculin reactors were in the far advanced stage. A higher proportion of the cases discovered among associates of reactors had tuberculosis in a far advanced stage.

As would be expected, those schools that had active tuberculosis cases in attendance had a much higher tuberculin reaction rate than those which did not; almost twice as high, in fact.

All but three of the 29 active cases of tuberculosis found and reported by the nurses—22 among reactors, 7 among associates of reactors—were admitted to sanatoriums. Herein, it is felt, lies an important consideration in recommending the tuberculin testing and x-ray technique of case-finding. Since it offers a greater measure of control, particularly in a school system, cases can be followed more systematically toward completion.

The present study was not planned in advance of the tuberculin skin testing programs carried on by the 49 nursing services. The programs conducted by these 49 services were largely autonomous, and therefore are somewhat lacking in uniformity of reporting. Yet their findings suggest several conclusions:

1. Quite aside from its educational value, the tuberculin test and x-ray screening technique in schools has a demonstrable value in case-finding.
2. Cases found in schools through this method are uncovered in an earlier stage of the disease than through the traditional physician-patient relationship.
3. School programs of skin testing and x-raying, by their very nature, make possible a relatively complete followup of suspected cases and placement of active cases under sanatorium care.
4. A great proportion of persons tested are non-reactors, and therefore need no further immediate study, thus making possible more intensive differential diagnosis of individuals in the reactor group.
5. Through x-ray followup of family associates of reactors, active cases may be found among parents and family members.

The tuberculin testing technique, as J. Arthur Myers has pointed out, has been brilliantly successful in eradication of tuberculosis among cattle. Its full potentialities in the eradication of tuberculosis among human beings, the present writers believe, have been insufficiently realized.

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Only by the discovery and treatment of the early case can the ultimate conquest of tuberculosis be effected. Mass x-ray surveys have contributed immeasurably toward this end. At the same time the number of new-found cases, coupled with the decided decrease in the disease mortality rate, has created an increased need for additional beds. That need has now reached alarming proportions and constitutes a major problem in tuberculosis control. J. Winthrop Peabody, M.D., J.A.M.A., December 13, 1952.

A Plea for Greater Use of the Tuberculin Test in the Eradication of Tuberculosis

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Tuberculosis is a disease that has caused much suffering and hundreds of thousands of deaths over the past centuries. No progress was made in its treatment or prevention until Robert Koch discovered the tubercle bacillus in 1882, marking the first real advancement made in controlling this disease. While this disease was called the disease of youth, in the light of present knowledge we suspect that it caused deaths of older people just as it does today. The aged were dying as chronic cases, but death was attributed to other causes, such as chronic bronchitis, bronchiectasis, or congestion of the lungs. When the tubercle bacillus was first discovered it was thought that only a matter of time would elapse before a cure would be found, or at least a way to protect the public. Since then many predictions have been made as to just how soon tuberculosis could be eradicated. The time usually given is from 15 to 20 years from the advent of each new treatment or method of handling the disease. Forty or fifty years ago, with the start of the sanatorium movement, it was predicted that tuberculosis could be wiped out in twenty years if sanatorium beds were provided for those having the disease. While the predication that the disease could be wiped out in a short time did not prove true, the sanatorium has contributed more than any other measure thus far, to the lowering of the death rate. The difficulty of discovering those who had the disease was not considered at that time, and it is still one of our greatest problems.

Just a few years ago I heard a talk in which the speaker prophesied that if a large amount of money was spent annually, the end would come in twenty years. In the last few months I have heard the prediction that with the use of surgery and the so-called miracle drugs the end would come in the next fifteen years or less, and that sanatorium treatment would not be needed. These prophets, unfortunately, must have a limited knowledge of the disease for many things other than one or two forms of treatment will have to be used in order to win the fight against tuberculosis. Those of us who have worked with this disease over a long period of time know that even now we cannot anticipate the length of time it will take to wipe out tuberculosis.

Yet great things have been accomplished in lowering the death rate from tuberculosis. In some places the rate has been reduced to only one-fifteenth or one-twentieth of what it was thirty years ago. This is a great accomplishment but we must not relax our efforts. The end of tuberculosis is still a long way off and the final eradication is not going to occur during the present generation. Every person who is infected with tuberculosis either by exposure to the disease or by artificial means is a potential case of tuberculosis for the rest of his life. Proper care, using the means and knowledge we now have, will prevent many of these people from breaking down, so that in their lifetime they may see the present low-death rate greatly reduced.

Koch thought he had a cure for tuberculosis when he developed tuberculin. Since then, many so-called cures have been produced and used, but none has been of real value and many have been harmful. Recently, with the discovery of the so-called miracle drugs, renewed hope has been raised. While it is too early to estimate their real value, it is felt that they are helpful when used with judgment and in conjunction with other means at our command, such as rest and surgical procedures in selected cases. Unfortunately they have raised a false hope in many and caused patients to feel that the use of these drugs alone will bring about recovery.

Tuberculin proved to be of little value as a curative agent, but it did become one of our most potent weapons in the fight against tuberculosis, not only in animals, but also in man.

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Unfortunately, the value of the tuberculin test has not been appreciated. It could have been used more extensively. The test is of value because it tells whether the patient does or does not have the germ of the disease in his body. It is important that the test be properly administered with potent tuberculin and correctly read. This is the first step in any good program for the eradication of tuberculosis. If the test is positive, it indicates that germs of tuberculosis are present. The next step is to determine by further examination whether these germs are causing clinical disease.

Thirty or forty years ago it was thought that from 80 to 90 per cent of the entire population had been infected with tuberculosis by the time age 15 was reached. These figures were reached as the results of tests made in the clinics of the larger cities where most of the children came from homes where tuberculosis existed. Naturally, under such conditions the number of reactors was large. It was felt that for the population at large this was an erroneous conclusion and it prompted a survey in the schools of the counties of the southwestern Minnesota sanatorium district which proved most interesting. At the start of the project the goal was set at 500 tuberculin tests. It was thought that this number would be sufficient to give a good cross-section of what could be expected in the school population, particularly in rural districts. As the work progressed the project proved so interesting and informative that it was not concluded with the proposed 500, but was continued until it had reached a total of more than 1600 tests, the greatest number reported previous to that time.

The findings were presented at a meeting of the National Tuberculosis Association in 1924. They were entirely different from all previous reports except in the case of those children who came from homes with a history of tuberculosis. Ten per cent of all those tested showed positive reactions but in children coming from homes where there had been tuberculosis, 81 per cent were positive. The value of the test was further demonstrated when it became apparent that when one child in a family reacted, usually others from that home did too. Another interesting observation was that when local physicians who knew the backgrounds of the children participated in the reading of the tests, they indicated that at least 50 per cent of those who reacted positively had some relative who died of tuberculosis or had the disease. Home investigation of other reactors showed many unsuspected cases of tuberculosis. Not only was the infected child discovered but also the trail of the infecting person. So the test proved to be a most valuable agent in the fight to eradicate tuberculosis.

Localities where this method has been used have had excellent results and are usually far ahead of those using other procedures. Our plan in the southwestern Minnesota sanatorium district is to test annually the first, ninth and twelfth grades in our schools. Unfortunately, lack of help has prevented our carrying out this plan completely. The testing of the first grade is not for the purpose of finding tuberculosis in the child, but to locate a possible source of infection. When one finds a young child with a tuberculin reaction it is likely that he became infected by a person in his home or in the comparatively small group of his close associates. An investigation of the home often reveals the source of infection fairly easily. The possibility of finding the source decreases as the age of the child increases, for the older the child the greater is his chance of having been in contact with a tuberculous person outside the home, possibly many miles distant. Efforts to find the source of infection have proved worth-while. The daughter of a patient recently admitted to the sanatorium reacted positively two years ago. At that time, on the advice of the public health nurse who visited the home, this patient was examined and the x-ray showed evidence of what was considered to be a healed lesion. She was advised to keep herself under observation, which she did, and only a few weeks ago the disease became active. She is now being successfully treated. It is reasonable to feel that this patient had been an open case previously, at which time the daughter became infected, but the disease became quiescent only to become active later when conditions were right. This patient could have become a far-advanced case before being found had it not been that the daughter was positive to the tuberculin test and the mother kept under observation.

The use of the tuberculin test in schools as a means of case finding is by no means the limit of its usefulness. The x-ray picture of a patient recently admitted to the sanatorium showed what appeared to be a lesion with a cavity in the right apex. The patient came from a home where there were several childern living in crowded quarters, conditions ideal for infection if this had been a case of tuberculosis. These children were given the tuberculin test, but not one reacted. Knowing that the tuber-

culin was good, the test carefully given and properly read, we had irrefutable evidence that the patient did not have tuberculosis. Further study of the x-ray shadow simulating a cavity was done and a diagnosis of a lung cyst was made. The lung cyst was removed by surgery and the patient made an uneventful recovery. In this case the tuberculin test was of inestimable value.

Individuals frequently report for an examination because they have symptoms suggestive of tuberculosis and feel they may have the disease. None of the usual tests can confirm the diagnosis but it can be ruled out if there are children in the home who can be given the tuberculin test and are found negative. A child who is in contact with the patient makes a better test than a stomach-wash, guinea pig inoculation, or sputum examination. For the child who is in constant contact with the patient is more apt to reveal the presence of germs than any tests we may use.

When it is difficult to make a definite diagnosis on cases suspected of having tuberculosis, the tuberculin test is of great help. If it is given and found negative we can be reasonably sure that the patient does not have tuberculosis. If the test is positive it does not necessarily mean that the individual has clinical tuberculosis but indicates need for further study and close prolonged observation.

Over the years the family physician has done a great deal to bring the incidence of tuberculosis to its present low level. Most cases are discovered by him and referred to the sanatorium for treatment. I do believe, however, even more can be accomplished in finding early cases. The tuberculin test is simple, easy to administer and can be used by all physicians. It is my hope that it will be used more extensively by the family physician, for if tuberculosis is to be eradicated it will be largely through his efforts and interest. He is in the best position to do the most for he sees many patients who would otherwise not have a chance to be tested.

Minnesota is fortunate in that it has a low death rate from tuberculosis, consequently the percentage of positive reactors is very low. For this reason the tuberculin test is useful in all age groups. It was once thought that tuberculin would be useful only in testing children but we know now that it can be used with excellent results in the general population. Naturally the number who react positively increases as age advances. Two counties of our sanatorium district have been tested on a county-wide basis. Approximately 80 per cent of the entire population was tested, and about 25 per cent of them reacted positively. Less than 5 per cent of the school children reacted. Chest x-ray films were made of all positive reactors by the Minnesota Department of Health's mobile x-ray unit and all who showed shadows suggestive of disease were studied further to determine whether clinical tuberculosis was present. These first attempts to do county-wide surveys were very satisfactory. They gave proof that the tuberculin test can be used more extensively and with better results than was previously believed possible.

The death rate in the counties of the southwestern Minnesota sanatorium district was 51 per 100,000 in 1919, while in 1951 it was only three per 100,000. While the tuberculin test has not been used as extensively as desired, it seems to have played an important part in lowering the death rate. I believe it is safe to say that the end of tuberculosis is in sight but I won't predict any exact time. As long as there is even one person who reacts positively to the test, *tuberculosis has not been wiped out.* It will take the combined support and effort of all physicians, public health personnel, lay people, and agencies using all the methods we have and which may be developed to completely eradicate this disease.

However accurately we carry out the health examination of the community, we cannot expect to achieve complete victory over infection until the public itself has become better informed. It sometimes happens that an infectious form of primary pulmonary tuberculosis runs such a rapid course that others have been infected long before the next scheduled examination. A flare-up of an older tuberculous infection may also occur rapidly. Such cases are, however, not common and the patient is brought to bed very soon. In many cases the ignorance and asocial, sometimes antisocial, attitude of the sources of infection have contributed to the spread of infection. Tobias Gedde-Dahl, M.D., The American J. of Hygiene, Sept., 1952.

Report of Committee on Tuberculosis, American College Health Association

May 3, 1952

WILLIAM T. PALCHANIS, M.D.

Columbus, Ohio

THE TUBERCULOSIS COMMITTEE continues to keep before the colleges and universities of America the importance of tuberculosis control among college students because, as we know, tuberculosis continues to be the leading cause of death from disease in the college age group.

In May 1950, a double post card type of questionnaire was sent to 880 colleges. Replies were received from 582 or 66 per cent. Of the 582 colleges completing their questionnaires, 507 (86.5 per cent) reported using some type of tuberculosis control program.

In October 1951, a letter with a similar reply post card enclosed was mailed to 1050 colleges, an increase of 170 over the previous year. The information requested was the same as in 1950. Also enclosed in the mailing was a copy of the National Tuberculosis Association publication, *Is It TB?*, and attention was called to other materials available from state or local tuberculosis associations. Replies were received from 495 (47 per cent). Of this group, 422 (85.3 per cent) reported some form of tuberculosis case finding program.

In spite of the substantial increase in the mailing list of colleges to whom questionnaires were sent in 1951, there was a decrease in the number of replies received, and consequently, in the number of colleges reporting programs. However, the percentage reporting programs was practically the same each year, namely 86.5 and 85.3 per cent.

A number of factors may account for this apparent decrease. In 1951, the request for information was delayed much later than usual. Questionnaires were mailed in October rather than in May as in previous years. In addition to requesting information about tuberculosis case-finding program, the 1951 letter was much longer than usual, since it contained paragraphs about available educational materials and also called attention to the advantages of membership in the American College Health Association. It may be that in attempting to include so much in the letter, we failed to give sufficient emphasis to the return of the enclosed reply post card.

However, in comparing post card returns from the colleges for the two years, 1950 and 1951, we found that 211 of the colleges reporting tuberculosis control programs in 1950 did not reply in 1951. If we had heard from these 211 colleges, and if they had continued to have a tuberculosis control program, the total number of colleges reporting programs in 1951 would have been raised to 633, an all-time high. In other words, for the two year period 633 different colleges reported tuberculosis control programs, while the status of some 420 colleges remained unknown. Compared to the total of six colleges reporting in 1932, this means progress.

Presented with these facts, the Tuberculosis Committee realizes more than ever that it must continue in its efforts to stimulate and encourage good tuberculosis case finding programs in all our colleges. It intends to continue sending the questionnaire type of post card to obtain facts and figures about control programs. It intends to make up a list of the colleges reporting programs and to mail this to the colleges not having programs, as well as to those not replying to the questionnaires for the past two years. We hope that such a list will stimulate interest in the adoption of some form of case finding program. It also intends to furnish this latter

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Note: At this time, several slides were shown, illustrating schematically the unusually efficient facilities for mass chest x-ray and skin testing surveys at the Ohio State University Health Service, in order to demonstrate how one of our universities conducts a tuberculosis case-finding program.

TABLE I

PREVALENCE OF PREVIOUSLY UNKNOWN° TUBERCULOSIS IN A GROUP OF 584 COLLEGE STUDENTS WHO DID NOT PARTICIPATE IN REGULARLY SCHEDULED CHEST ROENTGENOGRAPHIC SURVEYS COMPARED WITH A GROUP OF 10,232 COLLEGE STUDENTS WHO DID PARTICIPATE

[From article in April 1952 issue of the American Review of Tuberculosis]

GROUPS STUDIED	PARTICIPATING OR VOLUNTEER GROUP		NONPARTICIPATING OR STRAGGLER GROUP	
Period of study	June 1949 to June 1951		June 1949 to June 1951	
Ages	18 to 42		18 to 24	
	Total	Per cent	Total	Per cent
Number of students examined	10,232	100.00	584	100.00
Number of students with active‡ tuberculosis	3	0.029	2	4.34
Known†	0	0.000	0	0.000
Unknown°	3	0.029	2	0.34
Number of students with inactive§ tuberculosis	28	0.27	18	3.0
Known†	19	0.18	13	2.2
Unknown°	9	0.087	5	0.85
Total number of students with previously unknown° tuberculosis	12	0.11	7	1.19

° The designation "unknown" tuberculosis refers to any form of pulmonary tuberculosis which was unsuspected, undiagnosed, unreported, and unknown to anyone previous to its discovery in this study.

† The term "known" tuberculosis refers to any form of pulmonary tuberculosis which has been diagnosed, reported, treated, and known to the student and others prior to this study.

‡ "Active" tuberculosis is used to designate characteristic pulmonary abnormalities observed on the chest roentgenogram associated with a positive cutaneous reaction to tuberculin, the presence of tubercle bacilli in the sputum or gastric contents, and recent symptoms.

§ "Inactive" tuberculosis is used to designate a stable pulmonary lesion associated with a positive cutaneous reaction to tuberculin, the absence of tubercle bacilli in repeated examinations of the sputum and gastric contents, and no symptoms.

group with information in booklet form on how to inaugurate and how to carry on a tuberculosis control program.

The Committee on Tuberculosis submits this report with a keen awareness of our task — to keep before the colleges and universities of America the need for programs of tuberculosis control. In spite of the apparent progress in treating tuberculosis with the newer drugs, it is still the conviction of the committee that the case-finding program is the first line of defense. "If you do not find tuberculosis you cannot treat it."

After viewing the facilities and seeing the methods employed, one might infer that the program at Ohio State is 100 per cent effective in finding all cases of tuberculosis among its enrollees. However, because participation in the program is a requirement which is not fully enforceable in all instances, the program is not 100 per cent effective. This is proved by the results of a study made at Ohio State and shown in table I.

The results of this study prove to all of us engaged in the search for tuberculosis that 100 per cent participation of all eligibles in a given survey is a must for 100 per cent effectiveness of the survey.

In conclusion, the committee wishes to express appreciation to the National Tuberculosis Association for mailing the questionnaire forms, for tabulating the data presented in this report, for arranging the exhibit on tuberculosis on display, and for making available the valuable services rendered by Miss Charlotte Leach, their consultant in health education.

MANY physicians are reluctant to believe that people can have pulmonary tuberculosis when they show no clinical symptoms and there is nothing to direct attention to their lungs except a shadow on a chest film. The tendency is to reassure the patient that the lesions are old and inactive, but the tragedy comes later when the same patient is found to have moderately or far advanced disease. Alan L. Hart, M.D., Public Health Reports, December, 1952

Tuberculosis in General Hospitals

From The Insurance Company's Viewpoint

B. E. KUECHLE

Milwaukee, Wisconsin

Every state adjudicates its claims of employees against industry under a compensation law. With few exceptions, hospitals, both public and private, are by statute compelled to be subject to the provisions of such laws.

By these laws, the employer (for the purpose of this discussion, the hospital) is required to pay medical expenses and compensation benefits in all cases of accidental injuries and death. In most states an employer must also pay the same benefits in cases of occupational disease. With the exception of large publicly owned and operated hospitals, practically all protect themselves against this liability by buying compensation insurance policies. Rates vary from state to state, depending on the benefit level in the laws.

Within each state, the rates are adjusted annually based on the actual experience of the previous two completed policy years. If the hospital is of sufficient size—in Minnesota it must pay an annual premium of at least $500—the actual experience of the hospital itself modifies the base rate either up or down.

Unfortunately, no figures are available which permit comparing costs of diseases among hospital employees with the cost of accidents. However, we are justified in making certain deductions from available statistics which satisfy us that the mounting cost of compensation insurance for hospitals is due entirely to the increased cost of diseases, primarily tuberculosis, and not to increased accident frequency or severity.

Casualty insurance statistics are maintained on what is known as a policy year basis. In other words, all policies issued during any one calendar year whether issued on January 1 or December 31 are included in one group. That means that at any one time two policy years are running concurrently, because, for instance, a policy issued on December 31 of any year would not expire until December 31 of the following year, whereas a policy issued on January 1 of the next succeeding year—the next day—practically runs concurrently with a policy issued on December 31, and still the figures are included in the subsequent policy year.

In Minnesota during policy year 1948, insured hospitals paid $155,551 in compensation premiums. In 1949, the next policy year, the premium payments amounted to $170,064. In 1948, losses totaled $86,143, representing a loss ratio of 55.4 per cent, but in 1949, the losses increased to $123,510, equal to a loss ratio of 72.6 per cent. The total payroll on which these premiums were based was $41,119,149 in 1948 and in 1949, $45,084,283. These figures include allowances for room and board.

During 1948, the loss ratio for *all* insured business, including hospitals, in Minnesota was 55.8 per cent and in 1949, the loss ratio was 59.7 per cent.

To further emphasize the adverse hospital experience compared with all other business, these figures are impressive. From 1942 to 1952, the last ten years, the compensation insurance rates in Minnesota decreased 23 per cent. This is true in the face of increased benefits granted by each biennial legislature during the ten years. During that same period, however, hospital rates for professional employees have increased by 44 per cent.

On January 1, 1951, rates for hospital professional employees were increased over the rates in effect in 1950 by 65 per cent in the face of a general increase state-wide for all other business of only 8 per cent. Naturally, these rate increases mean heavily increased operating costs for Minnesota hospitals.

For nonprofessional hospital employees, compensation insurance rates decreased 3 per cent during a ten-year period, compared with the 44 per cent increase for professional employees, indicating again the increased exposure to disease

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among professional employees. The payroll exposure for nonprofessional employees represents but one-fifth of the total hospital payroll.

According to the American Medical Directory of 1950, Minnesota had at that time 32,838 hospital beds of which 10,032, or 30.6 per cent, were in privately owned hospitals. We can assume that with few exceptions publicly owned hospitals are not insured. Their liability is assumed by the political unit operating the hospital. To be conservative then, and assuming the same picture is true throughout the United States as is true in Minnesota, approximately one-third of the total hospital payroll exposure is insured. The best actuarial computation which we have been able to make on a national level indicates an approximate annual hospital insured payroll of $1,100,000,000 and compensation losses of approximately $4,100,000. Carrying forward the comparison that one-third of the hospital business is insured, we, therefore, have an indicated payroll in hospitals in the country of approximately $3,300,000,000 per year and losses of $12,300,000 per year.

There is no reason to assume that the public isn't going to become conscious of the poor health supervision of employees being maintained in most hospitals. Those states which do not now compensate for occupational diseases, will undoubtedly, because of the pressure of public demand, have corrective legislation before long under which employees in hospitals will receive benefits on the same basis they are now receiving such benefits for industrial accidents. Also, when nurses become more and more aware of their rights under already existing laws, we may assume that claims will increase in number and cost materially. Hospital administrators will realize from these figures that the mounting costs for compensation insurance cannot be ignored.

It seems unfortunate that the necessity of protecting employees in hospitals from exposure to disease, primarily tuberculosis, should be awakened primarily because of mounting compensation insurance costs.

In 1941, in an article on "A Tuberculosis Control Program" published in the American Journal of Public Health, Dr. Plunkett of New York made this statement, "During the past five years the New York State Insurance Fund has expended more than $900,000 for medical and nursing care and compensation for 120 cases of tuberculosis which were declared compensable, and which had developed among 17,000 employees of the Department of Mental Hygiene."

Doctors Riggins and Amberson reported some time ago that in most nursing schools associated with large general hospitals from 75 to 100 per cent of the students who entered with a negative tuberculin reaction, acquired a positive reaction during training.

The cost factor, however, is not the only one which must be considered in discussing this problem. In the face of the already existing shortage of nurses, young girls are becoming fearful of this hazard of tuberculosis and may become reluctant to take nurses' training courses. Parents, as they become aware of the danger, may discourage and even prohibit their daughters from following this profession.

The answer to the problem is simple—hospitals must, as a minimum standard, follow the recommendations for tuberculosis control among employees recommended by the American Hospital Association.

HEALTH education of the public . . . is often considered the responsibility of organized voluntary and official community agencies. Of course, it is also the physician's personal responsibility. He certainly should educate his patients and their families and do what he can as part of the community program. Health education methods have changed materially in recent years, with much greater emphasis on community organization and on helping the people to help themselves. Hugh R. Leavell, M.D., The New England J. of Med., December 4, 1952.

The Role of the General Practitioner in the Treatment of Tuberculosis

W. L. MEYER, M.D.
Sanator, South Dakota

It must be appreciated that there are a limited number of physicians specializing in the treatment of tuberculosis. In the average rural community the number of people with active tuberculosis is not large and so the physician located in such a community has limited opportunities for observing this condition.

In the vast majority of instances the general practitioner is the one most closely associated with the patient, and the one to whom the patient will first turn when he feels that there is something wrong. It is only by constantly keeping in mind that tuberculosis exists and that it may appear in any person, young or old, that the general practitioner may detect the disease in its early stages when there is good opportunity for recovery and before any great amount of permanent damage has taken place.

There are certain symptoms that demand a thorough examination of the chest, including not only an x-ray film, but also a sputum and physical examination. Certainly the x-ray film can tell us a lot about the condition of the chest. It, however, will not detect all cases of tuberculosis of the chest and for this reason, physical and laboratory examination must not be neglected. Any change in the character of breathing, any persistent cough, any asthma, and any pulmonary hemorrhage, however slight, should demand inspection. We, who are working with tuberculosis, see many patients who have had symptoms that should have demanded an x-ray film and complete examination long before they had it. Many of these people had been under the care of their local physician. We have seen one whose family insist that the local physician refused to have an x-ray film taken even though the mobile unit film showed pathology. The local physician, who sees the patient first, must be the one to make at least a tentative diagnosis of tuberculosis and the one to see that the patient secures adequate treatment.

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With the relatively small number of tuberculosis patients that the average practitioner will have under his care, it is improbable that he will have wide enough knowledge of the ramifications of this disease, the newer drugs developed for its control, to care adequately for these patients. The treatment, because of the nature of the disease, is prolonged. Isolation at home is often unsatisfactory at the best. Relatives and friends cannot appreciate that rest is still the prime factor in treatment and will not allow the patient rest. It is difficult to have another member of the family care for the patient, in such matters as baths and meals. The patient feels that the relative-nurse has enough to do and will, perhaps because he is reluctant to be an additional burden, take on more of his care than is consistent with his condition. Numerous patients still insist that it is impossible to take treatment at home. Institutional care of tuberculosis is still the only satisfactory answer to the problem.

During the last few years there has been much accomplished in the development of new drugs for the treatment of tuberculosis, also in discovering the usefulness of old drugs. At the present time dihydrostreptomycin or streptomycin in association with para-aminosalicylic acid appears to be most effective. It is felt that the dosage of streptomycin or the dihydro form may be materially reduced and now it is only administered twice or three times a week in 1 gram doses. PAS is used in conjunction with either form of streptomycin in a dosage of 4 gm. t.i.d. This combination is usually used over a considerable period of time. Much fewer reactivations are discovered if the regime is carried out for a period of a year. No present consideration of tuberculosis would be complete without mention of isoniazid or some of its forms. It certainly is not the wonder drug that the newspapers originally gave it credit for being. It does have a definite beneficial effect, but probably less than one of the forms of streptomycin and

(Continued on page 152)

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.*

Clinicopathological Conference

Minneapolis Veterans Hospital*

Edited by James F. Hammarsten, M.D.
Assisted by Robert I. Lubin, M.D. and Donald Fry, M.D.

PRESENTATION OF CASE

A 48-year-old farmer was admitted on July 7, 1950, because of fever for eight weeks. The fever occurred in the afternoon and evening and rose to 102° to 103° F. daily. For two weeks prior to admission the fever was accompanied by shaking chills and profuse sweating at night.

Five weeks before admission he had pain in both legs associated with swelling of the knees and ankles. He also had pain in the forearms. The pain and swelling subsided after three weeks. He also had a nonproductive cough, generalized nonpleuritic chest pain, malaise, anorexia and a 20-pound weight loss.

The past history was significant in that he had intermittent attacks of wheezing and dyspnea for six years and in 1942 had pleurisy that was relieved by taping the chest. The only significant family history was that a nephew had diabetes mellitus.

Physical examination disclosed a firm node in the right cervical chain. The liver and spleen were both palpable two finger breadths below the costal margin.

The temperature was 101.6° F., the pulse rate 88 per minute, and the blood pressure 126 mm. Hg systolic and 76 diastolic.

The admission laboratory studies showed hemoglobin 10 gm. per 100 ml., red blood cell count 4,790,000 per mm.,^{3} hematocrit 34 per cent, MCD 7.3μ, MCV 73 μ,^{3} MCH 21 $\mu\mu$, MCC 31 per cent, and a white blood cell count of 4700 with 71 per cent neutrophils, 28 per cent lymphocytes, and 1 per cent eosinophils. The bleeding and clotting times were normal, the reticulocyte count 2.2 per cent, and the platelet count 235,000 per mm.^{3} An erythrocyte sedimentation rate was 126 mm. in one hour. The blood Kahn was negative. The urinalysis was normal. The serum protein was 7.6 gm. per 100 ml. with 3.4 gm. albumin and 4.2 gm. globulin. The blood urea nitrogen was 8 mg. per 100 ml. and the urea clearance was normal. The bromsulfalein retention was 5.2 per cent in 45 minutes, the prothrombin time 19.1 seconds (control 13.5 seconds), the thymol turbidity 3.0 units, the cephalin flocculation negative in 48 hours, and the serum bilirubin 0.2 mg. per 100 ml. in one minute and 0.6 mg. total.

Several blood cultures were negative. The stools were negative for blood, ova, parasites, and pathogens. The agglutination titers for typhoid, brucella, and tularemia were not elevated. X-ray films of the chest were negative.

The lymph node was biopsied on July 10 and showed caseous tuberculosis with demonstrable acid-fast organisms. Bone marrow and liver biopsies were negative. Four sputum smears and cultures were negative for tubercle bacilli. The tuberculin skin test was positive using the first strength dilution.

The patient remained febrile with a temperature of 101° to 102° F. daily. Streptomycin, 1 gm. daily, and para-aminosalicylic acid, 12 gm. daily, were begun on July 19.

The patient showed no change for 2½ weeks except that his white blood cell count decreased to 2450 per mm.^{3} with 54 per cent neutrophils, 44 per cent lymphocytes, and 2 per cent eosinophils. His temperature then returned gradually to normal, his symptoms disappeared, and the sedimentation rate decreased to 58 mm. in one hour. After four transfusions of 500 cc. each his hemoglobin rose to 12 gm. per 100 ml. Glycosuria was noted August 1. The fasting blood sugar was 92 mg. per 100 ml. and the following results were obtained after oral glucose: ½ hour 188, 1 hour 266, 2 hours 177, and 3 hours 69 mg. per 100 ml. PAS was discontinued on August 18 and restarted on September 9. Both drugs were stopped on October 10. His sedimentation rate had decreased to 34 mm. in one hour. The white blood cell count was 2900 with 41 per cent neutrophils and 59 per cent lymphocytes. The serum protein was 7.2 gm. per 100 ml. with 4.6 gm. albumin and 2.6 globulin. The bone marrow showed a decreased number of cells in the neutrophilic series.

He remained asymptomatic and afebrile until December 24 when fever from 102° to 104° F. daily recurred and he again developed chills, weak-

*Published with approval of Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect opinion or policy of the Veterans Administration.

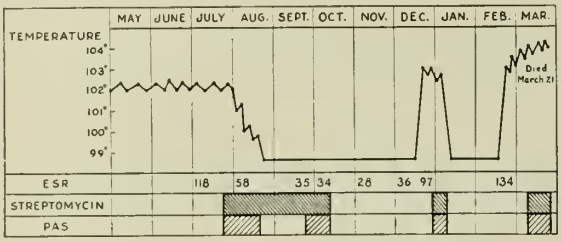

Fig. 1. Graph showing patient's response to therapy.

ness, and malaise. The liver and spleen had remained palpable. The sedimentation rate increased to 97 mm. in one hour and the white blood cell count was 3850 per mm.^{3} with 63 per cent neutrophils and 37 per cent lymphocytes. Streptomycin and PAS therapy was reinstituted on December 28. He became afebrile on January 6 and therapy was stopped.

On February 4 he again became febrile and developed erythema nodosum on both legs and erythema multiformi on the arms. A biopsy of the lesions on the legs showed inflammatory changes. The skin lesions disappeared in about three weeks but his temperature remained at 102° to 104° F.

On March 2 he began to have severe diarrhea. The hemoglobin had decreased to 8.9 gm. per 100 ml. and the white blood cell count to 1200 per mm.^{3} with 71 per cent neutrophils, 27 per cent lymphocytes and 2 per cent eosinophils. The erythrocyte sedimentations rate was 134 mm. in one hour. On March 8 streptomycin and PAS were again started. He was given several transfusions. A lumbar puncture showed normal dynamics and normal spinal fluid.

On March 9 he became confused and his abdomen became distended. X-ray films of the abdomen showed only gas-filled large bowel. Examination of the abdomen was negative except for distension. The gastrointestinal tract was intubated, and the patient was given parenteral fluids. The serum potassium decreased to 2.75 MEq per liter, but was increased by parenteral potassium. The electrocardiogram, which was previously normal, showed a prolonged Q-T interval when the potassium was low. The blood pressure gradually decreased to 68 mm. Hg systolic and 30 diastolic and the patient became stuporous.

During his hospital course 27 direct smears of the sputum were negative for acid-fast bacilli. Twelve concentrates of the sputum were negative and one on November 28 was positive for acid-fast bacilli. The sputum culture was negative on November 28 as it was on eight other occasions. Six gastric aspirations were negative by culture for acid-fast bacilli and one on November 18 was positive. Five urine cultures were negative for acid-fast bacilli on cultures as was the spinal fluid and bone marrow. Twenty-one x-ray films of the chest were negative. Gastrointestinal x-ray films after a barium meal and enema were negative. An excretory urogram was negative. The prothrombin time had remained persistently prolonged. Repeated urinalyses had all been normal except for occasional mild glycosuria.

His temperature remained elevated, but diarrhea ceased on March 14. The liver and spleen remained palpable. The bone marrow again showed decreased number of neutrophils. He died on March 21, 1951.

DISCUSSION

DR. WESLEY SPINK*: This man was well until eight weeks before admission when he had a sudden departure from health. The important features in the history are fever, shaking chills, pains in the legs, swelling of the knees and ankles, unproductive cough, chest pain, anorexia, weight loss, wheezing and dyspnea for six years, and pleurisy some years before. The notable physical findings were a palpable lymph node, hepatomegaly, and splenomegaly.

In approaching a case I try to decide what it could be after obtaining the history; and then after the physical examination should I add or subtract anything? After reading the history and physical findings in this case I thought of four things: (1) lymphoblastoma – Hodgkin's disease, (2) brucellosis, (3) tuberculosis and (4) actinomycosis.

There are some features in the laboratory data that immediately attracted my attention. First of all there is a leukopenia which would be consistent with any of the diseases I mentioned. With Hodgkin's disease I would anticipate a higher neutrophil count. The rapid sedimentation rate, leukopenia with normal neutrophilic percentage, chills and fever, and large cervical node suggest tuberculosis as the first possibility and Hodgkin's disease as the second. Brucellosis is ruled out with the negative agglutinin tests.

The lymph node was biopsied and it showed caseous tuberculosis with acid-fast organisms. One thing we are sure of. He had tuberculosis. I don't see how to escape tuberculosis as a possibility and at least give him a therapeutic trial of streptomycin, which was done. There was no change for 2½ weeks. That's a disturbing feature because usually there is a change within a week. Coincident with the drop in temperature is a decrease in sedimentation rate, and the albumin to globulin ratio returns to normal. I have drawn a rough diagram to show the relation of improvement to treatment with streptomycin (figure 1).

We have the following evidence for tuberculosis: (1) lymph node biopsy showing caseation, (2) leukopenia, (3) positive tuberculin test, (4) response to streptomycin, (5) erythema nodosum, (6) positive gastric washing, and (7) positive sputum. If this man proves to have something else, I will be extremely surprised. I believe he has generalized tuberculosis with miliary lesions in the spleen, liver, and probably kidney. I have no second choice.

A RESIDENT: What is your opinion of the glucose tolerance test?

*Professor of medicine, University of Minnesota.

(Continued on page 156)

Lancet Editorial

When Tuberculosis Begins

In the earlier years of the campaign against tuberculosis this disease was thought to begin when symptoms were in evidence. This opinion was current since the days of Hippocrates. With the extensive use of the x-ray film, beginning in the early 1920's, many persons were seen who had shadow-casting lesions which later proved to be tuberculous, yet there were no symptoms. Therefore it was said that the x-ray film was the earliest way to find tuberculosis at its beginning. Later, extensive and prolonged observation showed that x-ray evidence of tuberculosis often is not present until years or decades after the disease has actually been present, and in a great many people the x-ray film never reveals any evidence of disease, although it is found in abundance at necropsy.

Experimental work has revealed that tuberculosis actually begins within an hour after the invasion of tubercle bacilli. Within that time organisms introduced directly into the blood streams of animals have been phagocytosed by white blood cells (neutrophils) which have focalized them at many points in the body. The first illness occurs in these cells which ingest tubercle bacilli. The tubercle bacillus contains a substance (polysaccharide) which is poisonous to neutrophils. Each neutrophil which has ingested one or more tubercle bacilli very soon develops a fatal illness. This is first manifest by the neutrophil losing its ability to change its shape. Therefore when it arrives at the entrance of a small capillary, it cannot elongate and pass through as normal neutrophils do. The sick neutrophil is forced to remain at the entrance of the capillary. As it lingers and dies there, another kind of white blood cell (monocyte) appears in large numbers to completely surround the ill and dying neutrophil. As the dead neutrophil disintegrates, its particles containing the tubercle bacilli are ingested by the monocytes which remain at this point. Here, other well known changes occur in the formation of tubercle.

Focalization and subsequent tubercle formation occurs in many places in the body simultaneously. But this condition is often unappreciated. The large number of tubercle bacilli which enter with the first invasion could not possibly be ingested by a single neutrophil, and certainly not all neutrophils which ingest tubercle bacilli could be expected to fall ill and lodge at the same place. When illness occurs, they may be widely distributed over the body and are fixed at those points when they lose ability to change shape. Some may be in the brain, others in the spleen, or the liver, others in parts of the genito-urinary system such as the kidneys, some in bones and joints, etc. More are likely to lodge in the lungs than anywhere else because of their great volume and their numerous small capillaries. Thus the established foci of tubercle bacilli are multiple and any one or more of them may at some subsequent time result in destructive and incapacitating disease. Many persons develop such lesions in a kidney, an epididymis, a uterine tube, a bone or joint, the meninges, etc., without demonstrable evidence of pulmonary tuberculosis, and vice versa.

Since more original foci are established in the lungs than in any other organ, there are more potential clinical lesions there and hence, more clinical tuberculosis occurs in the lungs than elsewhere.

Thus tuberculosis begins within an hour after tubercle bacilli invade the body. Future happenings depend upon how much it evolves and at what sites. It continues to be tuberculosis at every step as long as tubercle bacilli are alive in the body.

During the first few weeks of the existence of tuberculosis, the tissues of the body, including the skin, become sensitive to the protein eliminated by tubercle bacilli. By special, but impractical methods, this sensitivity also known as allergy, can be detected within three or four days after the initial invasion of tubercle bacilli, but it can be detected by a most practical and accurate method within three to seven weeks of the beginning of the disease by the reaction to tuberculin.

When a serious effort is made to detect all tuberculosis as near the beginning as possible, much more rapid strides will be made toward the eradication goal than are possible by the

method now so generally used which finds the disease only after gross lesions have developed that cast the x-ray shadows.

Only a few of the numerous advantages of finding tuberculosis as near the beginning as possible can be discussed here.

1. When the disease is found by the tuberculin test as soon as the tissues have become sensitized, one has made the earliest possible diagnosis of tuberculosis. This is usually long before any symptom appears, or x-ray shadows are in evidence, or contagion is present. Knowing that tuberculous lesions containing tubercle bacilli, even though microscopic, are present places the physician on the alert and makes it mandatory that the individual, regardless of age, be kept under close observation for the earliest possible evidence of clinical lesions that may evolve. If the physician is watching for such lesions in the chest and elsewhere they are likely to be found much earlier than would otherwise be possible.

2. Finding tuberculosis by the tuberculin test soon after allergy appears enables the physician and the health officer to promptly locate the source of the infection in adult associates much more often than by any other method. If one waits for x-ray shadows or symptoms, the contagious case responsible may continue to disseminate tubercle bacilli for months and years before his disease is recognized.

3. By finding tuberculosis promptly after allergy appears the physician and the courts should be able to place responsibility for the individual's infection. In many places tuberculosis is now compensable for such groups as industrial workers, students, internes, residents and other employees of hospitals. The industry or institution that permits its employees, students or personnel to be infected in line of duty is in reality responsible for the clinical tuberculosis which may subsequently develop. Under laws and opinions now in vogue the responsibility for a case of clinical tuberculosis is frequently misplaced. All too often the organization or institution where the individual happens to be when an x-ray shadow-casting lesion is found, or symptoms appear, is declared responsible even though that concern had nothing whatever to do with initiating the disease or causing its evolution. For example, a student of nursing enters school as a nonreactor to tuberculin. In the course of training she is exposed to a contagious case of tuberculosis in her home, school, hospital, or in an institution where she is sent as an affiliate student nurse. Within three to seven weeks after the exposure she is found to react to tuberculin, indicating that she has tubercle bacilli-containing lesions. The x-ray films of her chest then and on graduation show no evidence of disease. One, five or more years later an x-ray shadow-casting lesion is found and proved to be tuberculous and the institution where she is then working is held responsible. The very nature of tuberculosis makes this a difficult problem. Often statutes of limitation free institutions of all responsibility after a few years. Moreover, it is perplexing for judge and jury as well as members of industrial commissions to comprehend that invasion with tubercle bacilli today may be responsible for the first demonstrable lesion by x-ray inspection or otherwise five, ten, or more years hence.

4. Much is said about treating tuberculosis early. To date this has applied for the most part to persons with gross lesions detected by x-ray film inspection. This is largely because no drug of proved value has been available for treatment of strictly early tuberculosis.

There is reason to be hopeful that a drug which will serve as a germicide may soon be available for this disease. It is even possible that methods may be found of administering our present drugs, including streptomycin, para-aminosalicylic acid and isoniazid so one or more of them will have a bacteriocidal effect. In any event, whenever such medication is available it may be expected to serve its best purpose in the beginning of tuberculosis. When an individual's tissues first become sensitized to tuberculin and for some time thereafter, lesions are usually small and vascular. No serious tissue destruction has occurred. A bacteriocidal drug administered at that time might be expected to reach all tubercle bacilli in lesions throughout the body and destroy them, thus completely curing tuberculosis. On the other hand, if one waits as is done at present, until gross lesions are detectable by x-ray film inspection, the lesions of the primary complex as well as the gross demonstrable lesions have greatly reduced vascularity and it could hardly be expected that tubercle bacilli would be reached and destroyed by a germicidal drug in the blood stream. We would still be compelled to subject persons to long periods of treatment, including various surgical procedures, none of which cures tuberculosis.

Finding tuberculosis when it begins and acting accordingly is the best known method of eradicating this disease.

Jay Arthur Myers, M.D.

You and Tuberculosis, by James E. Perkins, M.D., Managing Director, National Tuberculosis Association, and Floyd M. Feldmann, M.D., assistant to the Managing Director, National Tuberculosis Association, in collaboration with Ruth Carson. Alfred A. Knopf, publisher, New York, 1952. Pp. 176, price $2.50.

The material for this book was assembled by James E. Perkins and Floyd M. Feldmann, who graduated with the Medical School class of 1930, University of Minnesota. They immediately entered the field of public health. Dr. Perkins received the degree of Master of Public Health from Johns Hopkins University School of Hygiene in 1931 and the degree of Doctor of Public Health from the same institution in 1933. As epidemiologist of the Minnesota State Department of Health, Dr. Perkins conducted tuberculosis surveys and made a special study of this disease among Mexicans. He then became epidemiologist for the New York State Department of Health and later, director of the Division of Communicable Diseases. In 1946 he was appointed deputy Commissioner of Health in the state of New York. From 1937 to 1945 Dr. Perkins was associate professor of public health and preventive medicine, Albany Medical College. On January 1, 1948 he became managing director of the National Tuberculosis Association.

Dr. Feldmann, after graduating in medicine, accepted a position as epidemiologist with the State Board of Health of Minnesota, but in a few months took charge of a general hospital for Indians in Red Lake. In September, 1931 he was appointed epidemiologist for the Minnesota State Sanatorium — a unique position at that time. In 1933 he entered the Johns Hopkins School of Hygiene and Public Health as a fellow. A year later he became instructor in epidemiology in that institution, and in 1935 received the degree of Doctor of Public Health. He then resumed the position of epidemiologist with the Minnesota State Board of Health and was soon assigned to the directorship of the rural health unit at Mankato. After two years he was transferred to the unit at Rochester where, in 1941, he became health officer of that city. In 1948 he was medical director of central coordination and analysis office of the Tuberculosis Study Section of the United States Public Health Service, and in July 1949 was appointed assistant to the managing director of the National Tuberculosis Association.

Thus Dr. Perkins and Dr. Feldmann had extensive experience in tuberculosis control measures before assuming their present positions. These experiences, together with their numerous associations over the past few years with tuberculosis workers in this country and abroad have well qualified them for the preparation of this book.

Miss Ruth Carson, Brookfield Center, Connecticut, a popular writer on welfare and health subjects, collaborated in the preparation of this volume.

As the title indicates, this book is directed mainly to persons who have tuberculosis, and their families. The nine chapters contain much valuable information on pathogenesis, diagnosis, treatment, and prevention. The last chapter is devoted to research in which readers are given a glimpse into the methods of attacking the various phases of the problem.

This book can be highly recommended not only to those who have tuberculosis and their families, but to all who have any interest or in whom an interest in the disease may be created.

Certainly tuberculous patients who read this book will have impressed upon them the necessity of their complete cooperation with social workers, nurses, physicians and others who play any role whatsoever in their care. It should reduce the number of irregular discharges from our institutions and impress upon those whose disease is contagious the importance of preventing the spread of their tubercle bacilli to others, both in and out of institutions. This volume should also be read by all public health workers, including nurses and physicians, as it contains much information from which each one can profit.

J.A.M.

This Is Your World, by Harry A. Wilmer, M.D., Ph.D., edited by J. Arthur Myers, M.D., Ph.D. 165 pages. Springfield, Illinois: Charles C Thomas, 1952. $5.50.

The author intended this book to clarify, for professional workers, the emotional problems of the chronically ill, especially the patient with tuberculosis. He has succeeded admirably in fulfilling this purpose. The author is particularly well-suited for this task through personal experience and specialized training in neuropsychiatry. The volume is written in an informal and fascinating manner and was thoroughly enjoyed by the reviewer.

The emotional reactions of the patient to the original diagnosis, to the various phases of prolonged treatment and to the prospect of return to home and community are all discussed in narrative form with illustrative drawings. The author recognizes, only too well, the constant mental turmoil of the patient stricken with a chronic illness and the tremendous fortitude of spirit which is necessary to overcome the mental trauma. It comes as no surprise that many patients are not completely successful in adjusting to the overwhelming emotional strains that develop.

The author describes methods for recognizing the nature of the conflicts that arise and what to do about them. He discusses individual and group psychotherapy with appropriate warnings that the program should be directed by a trained and understanding physician. The chapter of illustrative dialogues, which may be used by the therapist in talks to patient groups at various stages of their stay in a sanatorium, is especially noteworthy. The writer emphasizes that therapy must always be aimed at allaying anxieties and never at arousing them.

The review of medical and psychiatric literature in the initial chapter and the discussion of the relationships between science and psychiatry in the final chapter serve to orient the reader to the problems treated in the main body of the book. There is also a selected bibliography and an adequate index.

This informative and interesting book is highly recommended to all professional workers who deal with chronically ill patients. S.S.C.

Program of the Sixty-sixth Annual Meeting of the North Dakota State Medical Association

YMCA, Minot, North Dakota

May 11 and 12, 1953

MONDAY, MAY 11:

8:30–9:30 Registration

9:30–10:00 *Recent Advances in Polio Therapy* — (speaker to be announced; courtesy North Dakota Polio Foundation)

10:00–10:30 *Fluid Balance* — Dr. K. G. Wakim, professor of physiology, Mayo Clinic, Rochester, Minnesota.

10:30–11:00 Intermission and view exhibits

11:00–11:30 *Facial Injuries* — Dr. Jerome H. Hilger, St. Paul, Minnesota

11:30–12:00 (to be announced) — Dr. George D. Davis, Department of Radiology, Mayo Clinic, Rochester, Minnesota

1:30–2:00 *You and the Draft* — Lt. Col. Matthew Stockton, 5th Army

2:00–2:30 *Congenital Heart Surgery* — Dr. R. L. Varco, Department of Surgery, University of Minnesota

2:30–3:00 *Carcinoma of the Cervix* — Dr. Willis Brown, chairman of Department of Obstetrics and Gynecology, University of Arkansas (courtesy of North Dakota Cancer Society)

3:00–3:30 Intermission and view exhibits

3:30–5:00 A Panel Discussion on *The Acute Abdomen.* Moderator—Dr. Richard L. Varco, surgery; discussors—Dr. Willis Brown, gynecology; Dr. K. G. Wakim, physiology; Dr. George D. Davis, radiology

MONDAY EVENING, MAY 11:

6:00 Special Society dinners and meetings

1. North Dakota Academy of Ophthalmology and Otolaryngology. Guest speaker, Dr. Jerome H. Hilger
2. North Dakota Diabetics Association. Guest speaker, Dr. C. F. Gasteneau
3. North Dakota Pediatrics Society. Guest speaker, Dr. Lewis Limarzi
4. North Dakota Radiological Society. Guest speaker, Dr. George D. Davis
5. North Dakota Obstetrics and Gynecology Society. Guest speaker, Dr. Willis Brown

8:00 Address by Mr. Frank Dickinson at the High School Auditorium, *Costs of Medical Care.* (This will be open to the public)

TUESDAY, MAY 12:

9:00–9:30 *Congenital Lesions of Kidney, Urethra and Bladder* — Dr. Norval O. Brink, Bismarck, North Dakota

9:30–10:00 *Traumatic Head Injuries* — Dr. L. A. Christopherson, Fargo, North Dakota

10:00–10:30 *Obesity* — Dr. C. F. Gasteneau, Department of Medicine, Mayo Clinic, Rochester, Minnesota

10:30–11:00 Intermission, view of exhibits

11:00–11:30 *Peptic Ulcer in Children* — Dr. Robert B. Tudor, Bismarck, North Dakota

11:30–12:00 *The Problem of Anxiety* — Dr. Gordon Kamman, St. Paul, Minnesota

1:30–2:30 Presidential address; inaugural address; introduction of 50 year Club members

2:30–3:00 *Hip Lesions in Children* — Dr. Carrol B. Larson, professor of orthopedic surgery, University of Iowa

3:00–3:30 Intermission and view exhibits

3:30–5:00 A Panel Discussion on *Anemias and Rh Factor.* Moderator—Dr. Lewis Limarzi; discussors—Dr. Robert B. Tudor, Dr. James D. Cardy, Dr. Robert B. Radl

Special Addresses

MONDAY, MAY 11:

10:00–11:00 Minot State Teachers College Convocation. Guest speaker, Lt. Col. Matthew Stockton, 5th Army

TUESDAY, MAY 12:

2:00–3:00 Minot High School Convocation, auditorium. Guest speaker, Dr. Gordon Kamman

Thirty-first Annual Meeting American College Health Association

Deshler-Wallick Hotel, Columbus, Ohio

Hosts: Ohio Section and Ohio State University

April 30, May 1 and 2, 1953

WEDNESDAY, APRIL 29, 1953

6:30 p.m.—Council Dinner—*Deshler-Wallick, Suite* 16

THURSDAY, APRIL 30, 1953

9:00 a.m.—Registration—*Foyer, Hall of Mirrors, Deshler-Wallick Hotel*

MORNING SESSION—10:00 TO 11:45 A.M.

Hall of Mirrors

10:00 a.m. Call to Order. Invocation. Welcome and orientation — J. W. Wilce, M.D., local chairman. Report of Secretary-Treasurer, Edith M. Lindsay, Ed.D., School of Public Health, University of California.

10:15 a.m. President's Address—Max L. Durfee, M.D., Director Oberlin College Health Service.

10:30 a.m. Panel—"Pressing Problems in Student Health Service." Chairman: Ralph Canuteson, M.D., Director University of Kansas Health Service. "The Constitution—Is Revision Necessary?"

10:45 a.m. Irvin W. Sander, M.D., Director Wayne University Health Service. "The Proposed Physician Training Program."

11:00 a.m. S. I. Fuenning, M.D., Director University of Nebraska Health Service. "Grass Roots Developments—The Present Status of the Local Sections."

11:15 a.m. Norman Moore, M.D., Director Cornell University Health Service. "The Health Service Survey—Progress Report."

11:30 a.m. Discussion.

GROUP LUNCHEONS—12:00 TO 1:30 P.M.

1. College Nurses—*Parlor H.*
   Section Chairman: Mrs. Mildred Crane, R.N., Otterbein College. *Luncheon Chairman*: Max Durfee, M.D., Oberlin College. *Speaker*: Paul Schumacher, M.D., Director Miami University Health Service. "Menstrual Pain — Older and Newer Therapies."
2. Larger College Administrative Round Table—*Ionian Room.*

Chairman: Dana L. Farnsworth, M.D., Medical Director Massachusetts Institute of Technology. *Discussion Leader*: Herbert R. Glenn, M.D., Director Pennsylvania State College – Chairman Committee on Administration. "Current Administrative Questions"—including Fees, Costs, Benefits.

3. Smaller College Administrative Round Table. *Parlors I and J.*

Chairman: George Blydenburgh, M.D., Director Health Service, Ohio Wesleyan University. *Discussion Leaders*: J. W. Hansen, M.D., Director Health Service, Carleton College. John McCleery, M.D., Director Health Service, Muskingum College. Otto J. Keller, M.D., Northern Illinois State Teachers College. "Current Administrative Questions."

AFTERNOON SESSION—2:00 TO 4:15 P.M.
Hall of Mirrors

2:00 p.m. "Anal and Rectal Conditions"—Color Film. Robert M. Zollinger, M.D., Professor and Chairman Department of Surgery, Ohio State University.

2:45 p.m. "Relationships of Oral Disease to Systemic Disease and Preventive Methods." Hamilton B. G. Robinson, D.D.S., Professor and Associate Dean College of Dentistry, Ohio State University.

3:05 p.m Discussion.

3:15 p.m. Nurses Symposium. "Current Correlations of Responsibilities of Nurse and Physician in College Health Services." *Chairman*: Mrs. Mildred Crane, R.N., Otterbein College. *Moderator*: Mrs. Rena Coppess, R.N., Wittenberg College

1. "The Smaller College with full time Physician." Mrs. Ruth Dutton, R.N., Miami University. Mrs. Bertine Long, R.N., Ohio University.
2. "The Smaller College with part time Physician." Mrs. Opal Thorpe, R.N., Western Michigan College of Education. Miss Gayle Pond, R.N., Central Michigan College of Education.
3. "The Cornell Cold Clinic." *Moderator*: Max L. Durfee, M.D. Norman S. Moore, M.D., Director Cornell University Health Service. Mrs. Frances McCormick, R.N., Cornell University. Discussion.

EVENING SESSION—6:30 TO 9:00 P.M.
Ohio College Health Association Dinner
Open to all members American College Health Association
Hall of Mirrors

Chairman: Max L. Durfee, M.D., President of Ohio College Health Association

Barber Shop Quartette Entertainment—The Buzz Saws.

Introduction of speaker by N. Paul Hudson, Dean of Graduate School, Ohio State University. *Speaker*: E. Herndon Hudson, M.D., Director Ohio University Health Service. *Subject*: "Fifteen Years of Medicine in Syria and Iraq." Illustrated.

9:00 p.m. Meeting of Mental Hygiene Committee. *Chairman*: Lewis Barbato, M.D., University of Denver.

FRIDAY, MAY 1, 1953
MORNING SESSION—9:00 TO 11:15 A.M.
Hall of Mirrors

9:00 a.m. "Autonomic Nervous System"—Color Movie, courtesy National Foundation for Infantile Paralysis.

9:40 a.m. Background of Emotional and Mental Hygiene Problems in College. Theodore C. Allenbach, M.D., Associate Professor Preventive Medicine and Psychiatrist University Health Service. *Discussion*: Lewis Barbato, M.D., University of Denver—Chairman Mental Hygiene Committee.

10:15 a.m. Influenza Symposium. *Chairman*: Warren Forsythe, M.D., Director Health Service University of Michigan. "Clinical and Therapeutic Aspects" Samuel Saslaw, M.D., Associate Professor Medicine and Assistant Professor Bacteriology and Preventive Medicine, Ohio State University. "The First College Influenza Immunization Program and our Six Years Experience." John Holland, M.D., Director Michigan State College Health Service. *Discussion Leader*: Ralph Canuteson, M.D., Director Health Service, University of Kansas.

11:20 to 11:30 a.m. Buses furnished by Association leave West Broad Street entrance of Deshler-Wallick for Ohio State University Campus—*Ohio Union.*

ASSOCIATION LUNCHEON—12:00 TO 1:30 P.M.
East Ball Room, Ohio Union
Ohio State University Campus

Chairman: Max L. Durfee, M.D.

12:05 p.m. *Invocation*: Malcolm McLean, D.D., University Religious Coordinator.

12:35 to 12:50 p.m. Ohio State Symphonic Choir.

12:50 p.m. Introduction of Past Presidents, Secretaries, and Honored Guests.

1:00 p.m. "New Horizons in Medicine." Richard L. Meiling, M.D., Associate Dean College of Medicine, Associate Director University Health Center, Brigadier General United States Air Force Reserve.

1:30 p.m. Recess. Inspection New Student Union.

AFTERNOON SESSION—2:00 TO 4:00 P.M.
Conference Theatre, Ohio Union

2:00 p.m. "Blood Dyscrasias of College Students with particular reference to Infectious Mononucleosis and the Anemias." C. A. Doan, M.D., Professor of Medicine, Dean College of Medicine, Director Medical Research, Director Ohio State University Health Center.

2:30 p.m. Discussion.

2:40 p.m. "Endocrine Problems and Therapies." George Hamwi, M.D., Professor of Medicine and Chairman of the Department of Endocrinology, Ohio State University.

3:00 p.m. Discussion.

3:10 p.m. Business Meeting, Reports, and Election of Officers.

4:00 to 5:00 p.m. President's Reception.
Faculty Club – Main Lounge
Convention members guests of the Ohio State University.

6:30 p.m. Council Dinner—*Faculty Club—Parlor E.*

5:00 to 8:00 p.m. Informal social period and facilities inspection opportunity. The facilities of the Faculty Club are available for those who wish to attend an evening round table and remain on campus in the interval. An informal meal will be served at the Faculty Club at 6:15 p.m. for those who care to make reservations.

AVAILABLE INSPECTION TRIPS
Short Walks

5:00 to 6:00 p.m. Present Health Service facilities and unusually efficient facilities for mass tuberculosis and mental hygiene and other surveys—Baker Hall, N.E. Wing (6000 sq. ft.). New Health Service facilities (in course of construction)—Student Services Building (16,000 sq. ft. – for occupancy August 1, 1953).

7:00 to 8:00 p.m. Main University Health Center. A visit to the outstanding Physical Medicine Department in University Hospital is suggested.

(Continued on page 157)

American College Health Association News . . .

Dr. Joseph Ritenour, a member of the honorary council of the American College Health association, died December 16 at the age of 37 years. Before his retirement in 1946, he had been director of the student health service and athletic team physician at Pennsylvania State college for 29 years. Dr. Ritenour served as president of the American College Health association for the years 1942 and 1943.

* * *

There will be a position available for a woman physician in the student health department of the University of Florida, beginning with the fall semester, September 14, 1953. Please direct inquiries to Sanford E. Ayers, M.D., director, University Infirmary, Gainesville, Florida.

* * *

Gallaudet College, Washington, D. C., has been accepted for membership by the executive committee. This college is subsidized by congress and is the only college in the world for deaf students. There are 140 men and 110 women enrolled. The health department is staffed by Mary C. Van Pelt, R.N., the full-time nurse, two part-time physicians and specialists in all fields. Miss Van Pelt attended the last annual meeting in Boston.

* * *

Anne Redman, R.N., secretary-treasurer of the North Central section, has forwarded a report of the fourteenth annual meeting of the section. The meeting convened for two days in October at Northfield, Minnesota, with Carleton and St. Olaf colleges acting as host schools. Roy Rueckert, M.D., University of Wisconsin, presided as president of the section. The delegates adopted a revised constitution, raised the dues from $1.00 to $2.00 annually, reactivated the committee on health education, organized a permanent committee of the nursing group, and accepted the invitation from the University of North Dakota, Grand Forks, to hold the 1953 meeting there. The following officers were elected: President, Dr. Donald Cowan, University of Minnesota; vice-president, Dr. Lois Boulware, State University of Iowa; secretary-treasurer, Anne Redman, R.N., Iowa State college. The program included the following:

"Emotional problems of the college adolescent"—Ralph Berdie, Ph.D., director, Student Counseling Bureau, University of Minnesota.

"Present trends in chemotherapy of tuberculosis"—Dr. Ezra Bridge, director, Mineral Springs Tuberculosis Sanatorium, Cannon Falls, Minnesota.

"Gynecological problems in the college age group"—Dr. James Shandorf, Minneapolis, Minnesota.

"Skin diseases in college students"—Dr. Elmer Hill, Minneapolis, Minnesota.

"Eye diseases in college students"—Dr. John McNeil, St. Paul, Minnesota.

"Orthopedic problems in the college age group"—Dr. Donovan McCain, St. Paul, Minnesota.

St. Olaf Hospital entertained the delegates at tea and Carleton College was the setting for dinner and evening entertainment. The meeting was attended by 44 delegates representing 30 colleges from Iowa, Minnesota, North Dakota, and Wisconsin.

* * *

Sanford E. Ayers, M.D., director of the department of student health, University of Florida, Gainesville, reports the addition of two new departments, namely, a psychiatric and a physical therapy service. Dr. James H. Closson, a psychiatrist with a number of years experience in student health work, was added to the staff in September. A representative student-faculty health committee, organized last year, has met a much needed liaison function between the health service and the rest of the university.

The outstanding event at the University of Florida during January 1953, from a health standpoint, was the influenza epidemic which affected at least 2,000 students. Soon after the first cases were seen, arrangements were made with the Communicable Disease Center of the United States Public Health Service to study the causative virus. Cultures were made of blood, stool, and throat specimens at the virus laboratories in Montgomery, Alabama, which later reported that the outbreak was due to Influenza A Prime. The medical staff of the University infirmary is making a study of the epidemic with particular reference to the efficacy of different types of treatment.

* * *

The executive committee at its recent Chicago meeting voted to instruct the secretary to inform Dr. A. J. Carlson, president of the National Society for Medical Research, that the American College Health association agrees with the principles of the society and desires to give support to the activities of the organization by means of channeling information to college students in health education classes. The society conducts an educational program directed toward the removal of obstacles to medical research. Members of the association may help in this program by utilizing opportunities to further public understanding of the methods of biological research. Publications may be secured from the society at 208 North Wells St., Chicago 6, Illinois. A film on the use of animals in medical research is now in production by the society. The officers are: President, Dr. Anton J. Carlson, professor emeritus of physiology at the University of Chicago; vice-presidents, Dr. Maurice Visscher, head of the department of physiology, University of Minnesota; secretary-treasurer, Dr. Andrew C. Ivy, vice-president of the University of Illinois.

RESULTS OF MINIATURE CHEST X-RAY PROGRAM

(Continued from page 126)

CONCLUSIONS

1. The North Dakota miniature chest survey program is one of the best organized and most successful programs of this type in the United States.

2. The outstanding success of the program is due to the complete cooperation between the Private Physicians, the Radiologists, the state health department, the U. S. Public Health Service, the state medical association, and the state tuberculosis association.

3. The program has been successful in detecting a large number of unsuspected cases of pulmonary tuberculosis, chest tumors, cardiac pathology, and other pulmonary conditions.

News Briefs . . .

Minnesota

DR. WILLIAM F. SCHERER, assistant professor of bacteriology and immunology at University of Minnesota, has been named recipient of a $30,000 teaching and research grant. He is one of 21 medical men who will benefit from $630,000 in grants from the John and Mary R. Markle foundation. Dr. Scherer will receive $6,000 annually for five years, the money to be used in medical research as he sees fit.

* * *

DR. WALTER WELLS, president of the Southwestern Medical Association was injured recently in a car-truck collision near Jackson, Minnesota, while on a sick call.

* * *

DR. OLGA S. HANSEN LITZENBERG was elected chief of staff of Eitel hospital, Minneapolis at the annual meeting of the hospital medical staff. Dr. G. T. Schimelpfenig was elected assistant chief of staff and Dr. O. L. Zahrendt, secretary-treasurer. Honorary life memberships to the staff were presented to Doctors S. Marx White, William H. Condit, Arthur C. Strachauer, Alfred T. Baker, Hugh H. Tunstead, and Henry L. Ulrich.

* * * *

DR. LEONARD A. LANG is now chief of staff at St. Mary's hospital, Minneapolis, and Dr. Horatio B. Sweetser is vice president and Dr. James Trow, secretary-treasurer. The medical advisory committee includes the officers and Doctors T. J. Kinsella, Maurice McInerny and Willard D. White.

* * *

NEW OFFICERS of the Hennepin County Medical Society are Dr. John H. Moe, president; Dr. W. L. Herbert, vice president; and Dr. Conrad J. Holmberg, secretary-treasurer.

North Dakota

THE SIXTH DISTRICT medical society recently elected Dr. John T. Cartwright, Bismarck, vice president. He will fill the vacancy created by the resignation of Dr. Ernest Salamone, Elgin, who is leaving North Dakota for Illinois.

* * *

DR. IRA S. AB PLANALP of Williston will be North Dakota's guest of honor at the first western hemisphere conference of the World Medical Association to be held in Richmond, Virginia, April 23 to 25, in observance of the lengthening of life and the improvement of human health. Attending the conference will be a 75-year-old physician from each state, appointed by the governor. There will be a review of medical advances during the last three-fourths of a century.

* * *

DR. B. W. MALONEY, practicing physician in LaMoure since 1947, has been called to active duty in the United States army air force. Taking over his practice is Dr. Neville Turner of Winnipeg.

* * *

RIVERDALE HOSPITAL, for five years operated by the Benedictine Sisters of the Annunciation, is now operated by Dr. Hugh R. Davidson, government contract physician. The change took place in February when the Benedictine Sisters terminated their contract due to reduction in patient load. According to army engineers, the hospital will be operated on a non-profit basis, giving all physicians in the area equal access to the facilities.

* * *

DR. PAUL L. JOHNSON, Bismarck, has been certified by the American Board of Orthopedic Surgery.

South Dakota

DR. T. J. BILLION, Sioux Falls, will be South Dakota's guest of honor at the First Western Hemisphere Conference of the World Medical Association in Richmond, Va., April 23 to 25. He was appointed by Governor Sigurd Anderson to represent the state as the physician who will be 75 years old in 1953. At the conference delegates will relate the medical advances which have taken place during their lifetime.

* * *

DR. F. J. DILGER has opened offices in Scotland, S. D. A veteran of World War II, Dr. Dilger completed his medical education at Northwestern University Medical school and took his internship at Wesley Memorial hospital in Chicago.

* * *

DR. WILFORD E. MARTYN has left Aberdeen for a two-year tour of active duty with the Navy.

* * *

DR. RUDOLF ORGUSAAR is the new resident physician in Revillo. A graduate of Alexander University in West Germany, Dr. Orgusaar completed his internship at McKennon hospital in Sioux Falls.

* * *

DR. HAROLD LOWE, who recently completed his internship at the Cook county hospital in Chicago, and graduated from Northwestern University Medical school, has joined the medical staff of the Lowe hospital in Mobridge.

* * *

A CIVIC reception was held recently for Dr. Avots in Carthage where he will establish medical practice. Dr. Avots took his internship in Lutheran hospital in Watertown and has received his license to practice in South Dakota from the State Medical Board. He came to this country from Latvia.

Wisconsin

CONSTRUCTION work on a new $2,300,000 hospital unit to replace the present 90-year-old Main building at Mendota State hospital was started February 26 with a ground-breaking ceremony at the institution. The new hospital will have a capacity of 200 beds. It will be the first of two units included in long-range plans for the hospital, which call for another large building for chronic disturbed patients, to be built later. At the ceremony, talks were given by State Welfare director John W. Tramburg and Dr. Leslie A. Osburn, director of the Mental Hygiene division. First to take part in the earth-digging ceremony was Dr. William D. Stovall, Madison, Wis., chairman of the State Board of Public Welfare.

° ° °

THE KROHN CLINIC and hospital at Black River Falls, Wis., has announced the appointment of Dr. Ann Cenlis, Sheboygan, to the staff.

° ° °

TURTLE LAKE has obtained a resident doctor to fill the vacancy caused when Dr. A. C. Halberg entered military service. Dr. Louis H. Pfieffer, Cumberland, has taken his place. He is a graduate of the University of Wisconsin, 1951, and took his internship at St. Luke's hospital in Duluth, Minn.

Iowa

DR. DAN B. EGBERT has been elected president of the staff of Lutheran hospital, Dodge, Iowa. Other new staff officers are Dr. Paul L. Stitt, vice president, and Dr. W. R. Gower, secretary-treasurer. Speaker at the annual staff dinner where the elections took place was Dr. Elmer M. Ruston, Minneapolis.

Deaths . . .

DR. RUSSELL J. MOE, Duluth, Minnesota obstetrician and gynecologist died March 8 after a long illness. He was a member of the Duluth clinic for 25 years and chief-of staff-elect of St. Mary's hospital. Dr. Moe was 51 years of age.

° ° °

DR. EDWARD MOREN, 77, Minneapolis surgeon who formerly taught at the University of Minnesota, died February 28 in Swedish hospital. Dr. Moren served as assistant professor of surgery at the University medical school, associate chief surgeon of Minneapolis General hospital and chief of staff at Swedish hospital. He was a graduate of the University of Minnesota and did post-graduate work at the University of Vienna, in Berlin, and in Copenhagen.

° ° °

DR. FRANK P. FRISCH, 68, died in Willmar, Minnesota, March 8. He was born in St. James, Minn., and was graduated from the University of Minnesota medical school in 1914. His practice took him to Kimball and Gibbon, Minn., and to Bismarck, N. D., before coming to Willmar in 1928.

° ° °

DR. FRANCIS J. CROMBIE, 48, North St. Paul physician died suddenly March 8. He was stricken with a heart attack at his Lake Demontreville home. Born in Columbus, Wis., he had practiced medicine in the North St. Paul area for 20 years.

° ° °

DR. J. H. BARRETTE, who practiced at Lehr and Wishek, N. D., for many years died January 3. At the time of his death he was practicing in Milnor.

° ° °

DR. HARRY J. BARTRON, 71, Watertown, S. D., surgeon died March 14 at a Des Moines, Iowa hospital. He was en route to Florida on a vacation trip. Dr. Bartron had practiced in Watertown since 1909, and with another physician started the city's first hospital in 1911.

DIABETICS RECEIVE ISONIAZID – NOTHING HAPPENS

A small study of whether isoniazid is effective in the treatment of diabetes is discussed in correspondence published in the April issue (Vol. 67, No. 4) of *The American Review of Tuberculosis.*

Observing a sharp drop in the insulin requirement of diabetic patients with tuberculosis, Dr. Sidney J. Shipman of San Francisco, president of the National Tuberculosis Association, requested Dr. H. Clare Shepardson, also of San Francisco, to try insulin on diabetic patients who did not have tuberculosis.

Dr. Shepardson writes that five patients with moderately severe diabetes without other complications were given isoniazid over a period of three months but "in no instance was the diabetes affected, either favorably or unfavorably."

"The patients' feeling of well-being was not altered, and no influence was evident on the insulin dosage or on the control of the diabetes, or on the patients' weight," states Dr. Shepardson, who adds that, to be concise, "nothing whatever happened."

"It seems likely," he suggests, "that the favorable influence you (Dr. Shipman) noted on the diabetes in patients with tuberculosis resulted from the effect of the drug on the tuberculosis and not on the diabetes."

PYRICIDIN (ISONIAZID) IN THE TREATMENT OF PULMONORY TUBERCULOSIS

(Continued from page 121)

been in patients who have exhibited bacterial resistance to streptomycin or in whom streptomycin or PAS could not be employed because of important toxic or allergic reactions. Isoniazid may be given, in addition to streptomycin-PAS, in seriously ill patients when maximal chemotherapeutic effect is desired or when the results of treatment with streptomycin-PAS have not been completely satisfactory.

In our hands toxicity has not been an important drawback to its use but there are reports to indicate that extreme central nervous system stimulation with acute psychosis may occur. Use of the drug, therefore, is contraindicated in patients with epilepsy or with seriously disturbed emotional or psychoneurotic backgrounds. Dosages should be limited, except for purposes of investigation, to 3 to 5 mg. per kilo. or 150 mg. to 300 mg. per day.

Bacterial resistance can be demonstrated by laboratory methods in an appreciable percentage of cases within three months, when isoniazid is used alone. Since the clinical implications of this fact have not as yet been determined, it is recommended that streptomycin or PAS and, at times, both drugs, should be used concomitantly with isoniazid in an attempt to delay or prevent the development of bacterial resistance. Cooperative studies are now in progress by the U. S. Public Health Service and the Veterans Administration, Army and Navy, which should aid soon in the solution of this important problem.

Isoniazid or any other known chemotherapeutic agent recommended for the treatment of pulmonary or extra-pulmonary tuberculosis are only adjuvants. Other therapeutic measures, including routine sanatorium care and surgical methods when indicated, remain essential to obtain maximal therapeutic results.

SUMMARY

1. Isoniazid (Pyricidin) is a drug of great promise in the treatment of pulmonary tuberculosis.
2. Toxic or allergic reactions to isoniazid, while few in number, occasionally may be of serious import.
3. Tubercle bacilli appear to become increasingly resistant to isoniazid but the significance of this has not been determined clinically.
4. Further studies by many investigators are under way in an attempt to answer many unsolved problems.
5. Streptomycin-PAS still continues to be the standard form of chemotherapy in the treatment of pulmonary tuberculosis but isoniazid is used clinically in selected patients.

THE ROLE OF THE GENERAL PRACTITIONER IN THE TREATMENT OF TUBERCULOSIS

(Continued from page 140)

PAS. Any discussion of chemotherapy in tuberculosis would not be complete without a word of caution.

There are still many side reactions if these drugs are used over a period of time. Some of them are irreversible and insidious. If any of these three drugs are to be used for the treatment of tuberculosis over any period of time, it should be done in an institution. Drug resistance is still encountered and it is unfortunate if some condition should develop later that would require the use of these drugs. Loss of hearing and vertigo are possible side reactions. While these conditions may be excusable if they occur during the treatment of such a condition as meningitis, nevertheless they would be unfortunate if they developed during treatment of a condition that would have cleared up without the use of these drugs. I recall only too clearly a beginning vertigo in a child that was being tested by a cultist, who has now left the state. This child had a primary infection that was inactive from the radiological and clinical standpoint, nevertheless he was still receiving streptomycin and was developing vertigo, as the result of overtreatment of an inactive condition. The chemotherapy of tuberculosis is prolonged and fraught with potential dangers. It should be carried out in an institution where the patient is under constant supervision.

Once tuberculosis has been brought under control — and now we do not feel that it is ever cured — the assistance of the general practitioner again is brought into the foreground. He is responsible for the care of the patient. He advises, with the cooperation of the chest physician, about all chest conditions. He supervises periodic checkups. He advises and cares for all associated conditions. There are many questions that will arise with each individual case which cannot be answered categorically. Each patient is a law unto himself, and what he can or cannot do, will depend entirely on the patient and the many factors involved in his case, and not entirely on the amount of disease that he has had.

Postinstitutional care of those with pneumothorax or pneumoperitoneum collapse will of course depend on the condition of the patient at the time of discharge. Refills will be maintained. The amount of air and the frequency of each refill will be determined by the individual case.

ROUTINE THERAPY FOR INTERNAL HEMORRHOIDS

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THE OUT-PATIENT SERVICE FOR TUBERCULOUS INDIANS IN MINNESOTA

(Continued from page 129)

to have inactive disease. One case of moderately advanced tuberculosis was diagnosed in the clinic, two in the hospital. One of far advanced disease was diagnosed in clinic and four in the hospital. Two cases of pericarditis, two of genito-urinary tuberculosis and one pleural effusion were diagnosed in the hospital. In establishing the diagnosis the services of the clinician as consultant were utilized.

We hope that the out-patient service will prove of value in the treatment of tuberculosis among the Indians, but realize that many of the problems presented have barely been touched upon at the present time. We hope that the program has had some educational value and that the Indians themselves realize a little more the extent of the problem with which they are faced and that they also are aware of our sincere wish to be of assistance in its solution.

Too frequently we fail to realize that health education today stands in the same relation to the control of today's major health hazards as did sanitation and isolation to the control of yesterday's problems. Berwyn F. Mattison, M.D., Am. J. of Pub. Health, December, 1952.

TESTING HYDRAZIDES FOR TUBERCULOSTATIC ACTIVITY

Since the discovery that certain hydrazine derivatives of isonicotinic acid are active against the tubercle bacillus, tests have been continued to determine if other hydrazides also have anti-tuberculous qualities. Recent studies at the Squibb Institute for Medical Research, New Brunswick, N.J., are reported in the March issue (Vol. 67, No. 3) of *The American Review of Tuberculosis*, published by the National Tuberculosis Association.

Jack Bernstein, William P. Jambor, W. A. Lott, Felix Pansy, Bernard A. Steinberg, and Harry L. Yale of the Institute found several hydrazides of heterocyclic carboxylic acids showed activity against tuberculosis in the mouse. However, none, according to the investigators, was as active as isoniazid, or isonicotinic acid hydrazide, which has been in wide use as an anti-tuberculous drug for the past year.

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(Continued from page 142)

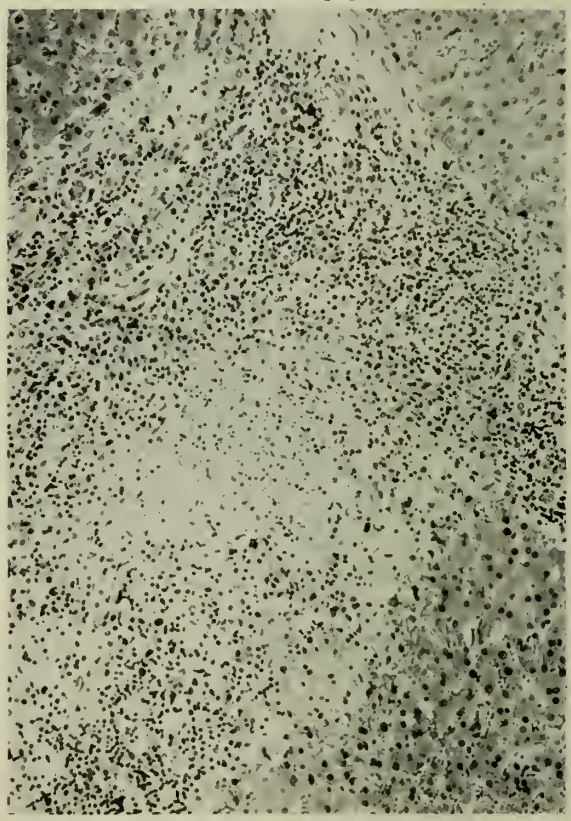

Fig. 2. Nodule in the liver with necrosis surrounded by lymphocytes and giant cells.

DR. SPINK: I would say it was an abnormal curve, but in a patient with this severe disease and weight loss I wouldn't interpret it as indicative of diabetes.

DR. HAMMARSTEN: There was a good deal of discussion about this case on the wards. Some thought as Dr. Spink does that he had generalized tuberculosis; others believed he had tuberculous adenitis with some other disease, such as Hodgkin's disease, in addition.

DIAGNOSES

Clinical diagnosis: Tuberculous adenitis, miliary tuberculosis? or Hodgkin's disease?

Dr. Spink's diagnosis: Generalized tuberculosis with miliary lesions in the liver, spleen, and kidney.

Anatomical diagnosis: Miliary tuberculosis involving the spleen, liver and mediastinal lymph nodes.

PATHOLOGICAL DISCUSSION

DR. GLEASON: There were several caseous lymph nodes in the mediastinum. The lungs were completely negative. The spleen weighed 340 gm. and was studded with nodules up to 4 mm. in diameter. The liver weighed 2400 gm. and showed similar nodules. On microscopical examination the nodules showed necrosis surrounded by lymphocytes and Langhans giant cells (figure 2). The findings indicate miliary tuberculosis.

(Continued on page 157)

DR. TUCKER: During the period this man was on our service we never made as much sense of the case as Dr. Spink has this afternoon. It was a confusing picture and I think it would be a mistake for any of us to say that we felt confident that he had generalized miliary tuberculosis, although we certainly considered it all the time. The basic problem is that we depend for our diagnosis of this disease upon the manifestations in the lungs, which are usually present, and upon bone marrow biopsy, which is positive in such a high percentage of cases. In this man both of these manifestations were absent.

ACHA PROGRAM

(Continued from page 147)

EVENING ROUND TABLES—8:00 TO 9:00 P.M.

Medical Health Center Hospitals

1. Chest and X-ray—Tuberculosis Hospital, Room 471. *Chairman*: William Palchanis, M.D., Chairman Tuberculosis Committee A.C.H.A. and Assistant Professor Departments of Medicine and Preventive Medicine—University Health Service. R. H. Browning, M.D., Professor Department Medicine and Director Ohio Tuberculosis Hospital. John A. Prior, M.D., Professor and Vice-Chairman Department of Medicine and Acting Chairman Department of Preventive Medicine.
2. Mental Health—Columbus Receiving Hospital, Room 034. *Chairman*: Lewis Barbato, M.D., University of Denver, Chairman Mental Hygiene Committee A.C.H.A. Ralph M. Patterson, M.D., Professor and Chairman Department Psychiatry and Superintendent Columbus Receiving Hospital and staff.
3. Cardiology—University Hospital, Room 419. *Chairman*: J. W. Wilce, M.D., Director and Professor of Clinical and Preventive Medicine—University Health Service. Joseph M. Ryan, M.D., Assistant Professor Medicine—Cardiology—University Hospital. Ray W. Kissane, M.D., Professor Department Medicine — Cardiology.

SATURDAY, MAY 2, 1953

MORNING SESSION—9:15 TO 12:00 M.

Chairman: Max L. Durfee, M.D.

9:15 a.m. "Wisconsin Report on Medical Aspects of Intercollegiate Boxing." John W. Brown, M.D., Director Health Service, University of Wisconsin.

9:30 a.m. Analysis of 1100 Minor Surgical Cases. Drew Arnold, M.D., Instructor Department of Surgery, Visiting Associate Surgeon—University Health Service, Ohio State University.

9:45 a.m. Recess

9:50 a.m. Symposium. "Health Insurance Plans for Colleges." *Moderator*: Ruth Boynton, M.D., Director Health Service, University of Minnesota. "Private Insurance Company Plans." Edward O'Connor, Chicago Representative of the Conference of Health and Accident Insurance Companies. "Blue Cross Doctors' Plan." Carl Munday, M.D., Toledo Executive Board, Ohio State Medical Association. "College Self Insurance Plans." Speaker to be chosen. Discussion.

11:00 a.m. Business Meeting and Committee Reports.

12:00 m. Adjournment of thirty-first annual meeting.

Classified Advertisements

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

A Symposium on Potassium Metabolism —Excerpts from Proceedings

Foreword . . . .

THE increasingly popular practice on the part of investigators in all branches of science of getting together periodically to inventory and re-examine their current stock of information on a specific subject has become an all but indispensable part of our general procedure for advancing technical knowledge. A symposium provides opportunity for a free and informal exchange of ideas, whether these are based upon the results of well-controlled experiments or upon the empirical observations of experienced workers in a field, and helps the individual participant to relate his own contributions to those of other workers in a manner most conducive to accurate work and critical thinking.

Experimentation in the field of potassium metabolism has been immensely facilitated by the availability during recent years of radioactive isotopes and flame photometry. As a result, data have accumulated at an inordinate rate. So comparatively new is much of our knowledge concerning the essential physiological roles and the clinical significance of body potassium, that no attempt has been made heretofore to bring the various aspects of the story of its development together. A superficial examination of titles for the three-day program devoted to the present symposium leaves no doubt regarding the need for this particular conference. Its sponsors, the M & R Laboratories and the University of Minnesota, wish to express their profound gratitude to the able participants and discussants for their invaluable contributions toward its success, and to THE JOURNAL-LANCET for publishing the proceedings of the meetings in abstract form.

IRVINE MCQUARRIE, M.D.
Chairman and Editor of the Symposium.
Head, Department of Pediatrics
University of Minnesota

The Metabolism of Potassium

A symposium presented by the University of Minnesota, Minneapolis, Minnesota, and sponsored by M and R Laboratories.

Edited by IRVINE MCQUARRIE, M.D.

[1953]

Contents:

EDITOR'S NOTE: Due to the large number of papers read at this symposium, it was found necessary to publish them in two parts. Part one appears in this issue and part two will follow in the June issue.

PARTICIPANTS IN THE SYMPOSIUM

JOHN A. ANDERSON,
Professor, Department of Pediatrics, Stanford University, San Francisco, California

PAUL D. BOYER,
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FRANK BRINK,
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HOWARD B. BURCHELL,
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WALTER S. WILDE,
Professor, Department of Physiology, Tulane University, New Orleans, Louisiana

MILDRED R. ZIEGLER,
Assistant Professor, Department of Pediatrics, University of Minnesota, Minneapolis

Introduction to a Symposium on the Metabolism of Potassium

WALLACE O. FENN, PH.D.
Rochester, New York

POTASSIUM is remarkable as the only ion of physiological importance which has a naturally occurring radioactive isotope, K^{40}. This isotope further on disintegration gives off beta rays and turns into Ca or gives off gamma rays and a positron and turns into argon. From the amounts of these substances the original amount of K^{40} can be calculated, as well as the age of the earth. With the original amount present there was enough heat from the higher rate of disintegration to keep the earth in a fluid state. Thus K is responsible for the formation of its own physiological antagonist, Ca, and has played an important role in the geological history of the earth.

Potassium is also remarkable as the essential intracellular cation. As such the exchangeable K of the soil is essential currency for the growth of plants and high K foods are essential for the growth of animals. This symposium is concerned chiefly with discussions of the rivalry between K and Na for a place in combination with intracellular anions and with the difficulties which occur in the animal economy when the K concentrations, either inside the cell or outside, become significantly deranged.

In considering the vagaries of K in the body, it is convenient to consider first the cell by itself. There are at least five different processes, as follows, which have been recognized as causing movements of K in or out of cells:

1. *The K inside is a function of the K outside.* Mammalian muscle cells are in equilibrium with a concentration of about 4 mEq/l in the plasma. At higher concentrations K enters the cells and at lower concentrations K leaves the cells. This has been demonstrated in perfused frog muscles[1] and in frog muscles dissected out of the body and suspended in solution. When KCl is injected into the solution it apparently enters the cells with H_2O and chloride as an isotonic solution of KCl in accordance with the Conway-Boyle theory.[3] Thus, injected K is distributed not in proportion to the pre-existing ratio between K inside and K outside, but is distributed rather evenly throughout all the H_2O of the body even though the total K is very unevenly distributed between intracellular and extracellular spaces. Why liver and other viscera appear to take up more than their appropriate share of injected K remains an unsolved problem.[4,5,17]

2. *K exchanges with H ions.* As the acidity outside the cells is increased, K comes out to neutralize the acid or it exchanges with the H ions.[2] Thus a higher concentration of K is needed outside for equilibrium if the solution is more acid. There is, in other words, a K shift out of the tissue cells under conditions which cause a chloride shift into the red cells. Both of these processes represent the mechanisms whereby the red cells or the tissue cells share their buffering capacity with the plasma. Of the two the K shift is of far greater importance because of the much larger volume of the tissues from which the K can be derived. This was first demonstrated for isolated frog muscles.[2] Rothstein and Demis[6] have recently shown that a similar relationship between K and H occurs in yeast cells.

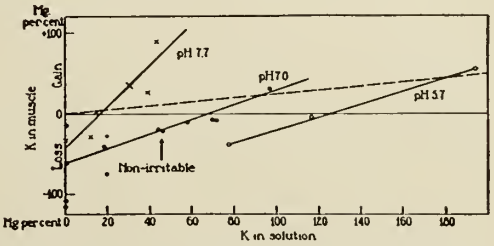

Fig. 1. Gain or loss of K by frog muscles immersed in hicarbonate-phosphate huffered Ringer's solutions of different pH and K content for five-hour periods at 22° C. and equilibriated with 5 per cent CO_2 in oxygen. The dotted line indicates the amount of gain to he expected from the K in the chloride space alone. The muscles become non-irritable due to the high K in concentrations above that indicated.[2]

This relationship between K and H is illustrated in figure 1. It represents an experiment in which isolated frog muscles were immersed for five-hour periods in solutions of different K content.[2] The paired muscle was analyzed for K in each case prior to immersion. The ordinates represent the amounts of K gained or lost by the immersed muscle. It is evident that there is a certain concentration at which the muscles neither lose nor gain K. At higher concentrations they gain K and at lower concentrations they lose K. Further at a lower pH a higher K concentration is required for equilibrium and the curve is shifted to the right on the diagram. These data are roughly in accordance with the equation:

$$\frac{Ki}{Ko} = \frac{Hi}{Ho}$$

The validity of this equation for human muscle in the body is not really known. It predicts that shifts of K represent the chief means by which acid base imbalances are equalized between tissue cells and plasma. Many cases could be cited in the literature where this apparently fails to occur, possibly because in the body the plasma K is also influenced by the kidney and other secretions. Pitts,[28] however, has recently reported that when alkali is

injected, chloride shifts between plasma and tissues in preference to K. This apparently does not occur in isolated frog muscles. The final answer to this problem remains for future investigation to decide.

When, however, the solution is acidified by raising the CO_2 tension, the situation is a little different because in this case acid is added both inside and outside simultaneously and the K then moves into whichever phase shows the greater decrease in pH. Using both nerves[8] and muscles[7] we have shown that if the outer solution is whole blood it is better buffered than the muscle so that an increase in the CO_2 tension drives K into the cells. If the outer solution is plasma or Ringer's solution, the same increase in pCO_2 causes the K to move out of the cell. Thus in the body hypocapnia, other things being equal, should bring K out of the cells and vice versa. This is not always evident in the body because of complicating factors such as renal stabilization, active extrusion of Na, or metabolic changes in lactic acid or phosphocreatine concentration. In general, acid arising outside the cell should bring K out, but acid arising inside the cell or a general rise in pCO_2 should bring K in. In either case the blood would indicate a condition of acidosis.

3. *Activity.* We were able to show sixteen years ago[9] that stimulation and contraction of muscle result in loss of K and gain in Na. This has been confirmed many times. During recovery the reverse process takes place. Recently Hodgkin and his collaborators[10] have shown that the same type of exchange occurs in nerve and they have established further in a very elegant series of papers, that the energy for the nerve impulse and its action potential is derived from the potential energy represented by the separation of K and Na between the inside and the outside of the cell. When the muscle or nerve is stimulated the membrane suddenly increases its permeability to Na and there is a rush of Na inwards which causes the upstroke of the action potential. This is followed by an increase in permeability to K and a K outflux which explains the falling phase of the action potential. During recovery the Na is pumped out by an active process of some sort, the "sodium pump",[11] and K is believed to diffuse back inside passively until its electrochemical potential inside and outside again reaches equality. The outflux of Na can never be passive because it requires movement, not only against the concentration gradient but also against the membrane potential, and at equilibrium the electrochemical potential is always higher outside. During muscular exercise the rise in plasma K may be due also to glycogenolysis in the liver. The rise observed is found to be diminished in trained athletes.[24] In cat muscles the loss of K on stimulation is not proportional to the number of nerve impulses delivered to the muscle for it is greater on intermittent tetanus (1 second tetanus, 4 second rest for 30 minutes) than with continuous tetanus for the same total period. The loss must depend in part upon the mechanical conditions of the contraction because it is greater in a muscle under isometric tetanus than in a muscle with the tendon cut. The loss is not linearly progressive with time because it may reach an early maximum and may even decrease thereafter. Potassium lost by an active muscle is taken up in part by inactive muscles, especially if the viscera are out of the circulation. If all the muscles of the body are active no muscle can lose much K because it has nowhere to go. Potassium is lost with voluntary as well as artificially elicited contractions.

Some studies have been made of the effect of stimulation on the K content of the salivary glands.[26] Electrical stimulation of the chorda tympani nerve causes a copious secretion of saliva containing considerable quantities of K but the gland succeeds in replenishing its supply from the blood as rapidly as it is lost to the saliva and the K content of the gland shows no change. With pilocarpine stimulation it is possible to deplete the K supplies of the gland. This is not due to diminished output of K in the saliva but rather to diminished intake from the blood.[27] The result is not in conflict, therefore, with the general proposition that activity involves loss of K.

4. *Sodium pump.* Since Na is continuously diffusing into cells, as can be demonstrated with radioactive isotopes, it is obvious that the Na pump must be continuously active. If this active extrusion proc-

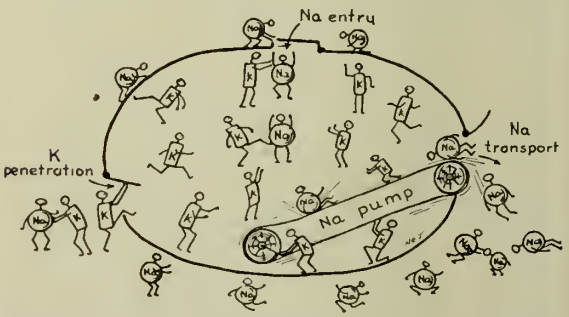

Fig. 2. Symbolic "Sodium Pump." (NOTE: So great was the mirth and interest created by this whimsical hut meaningful cartoon, when it was presented, that numerous requests for its publication were received. Aware of the fact that it is not all inclusive and that it represents hut one theory of electrolyte equilibrium, the author yielded to editorial pressure with great reluctance. Ed.)

ess diminished in rate, then intracellular Na increases and K diminishes. Presumably this is the case in red cells of dogs and cats which contain more Na than K.[12] The K levels inside and outside the cells therefore should depend in the last analysis upon the activity of the Na pump. So far we know little about this Na pump except that it appears to be geared to glycolytic rather than oxidative reactions. A beautiful model of an Na pump, however, is available for study in the frog skin where Ussing[13] has shown very elegantly that the current that can be drawn from the skin is exactly equal to the amount of Na transported. We have no information concerning the sodium pump in the body but there

can be no doubt that it is active and sooner or later we shall find pathological conditions which can be attributed to failure or overactivity of this remarkable Na-transporting mechanism.

It must be admitted that the evidence for a passive electrochemical K equilibrium, dependent indirectly upon the sodium pump, is not altogether convincing. Sodium and K do not always move reciprocally and it would be less venturesome and optimistic to postulate at the start a K pump in addition. Without denying the convenience and possibly the necessity of having two separate pumps it seems wise on general principles to postpone the adoption of a two-pump theory until all hope of doing the job with one pump has been completely eliminated.

5. *Metabolic factors.* Under this heading might be included a variety of factors including first the relation of K to carbohydrate.[16] This relationship is shown particularly well in the case of yeast[14,15] where the onset of glycolysis resulting from the addition of glucose to the medium causes an uptake of K. When the fermentation of this sugar is complete the K returns to the solution. Harris discovered similar occurrences in the red cell. In the body also K enters the cells from the plasma with sugars as they are taken up. Presumably it enters along with the water which accompanies the formation and deposition of glycogen as has been demonstrated in the liver. Under this head is also included the continuous loss of 1 gram of K for every 10 grams of N_2 which represents the basal metabolic breakdown of body cells[16] and the rise in plasma K with rise in metabolic activity (dinitrophenol) and body temperature.[20]

These seem to me the most important of the processes influencing the distribution of K in individual cells. Many other factors may come to mind, but in most cases they may be classified under one of the categories already mentioned or they have not been demonstrated on isolated cells.

In the body as a whole other processes, of particular importance for the understanding of variations in the K concentration of the plasma, must certainly be mentioned. Some of these are as follows:

1. *The absorption and the excretion of K.* In general the absorption depends upon the diet, while the excretion depends upon the kidney. Variations in plasma K occur in spite of the kidney or because of its failures. The plasma K may be low because the kidney is unable to reabsorb K from the tubules,[18] or it may be high because the kidney is unable to secrete K in the tubules. There is now ample evidence[19] that some K is secreted in the tubules and some believe that most of the filtered K is reabsorbed and that most of the K eliminated in the urine is actively secreted by the tubules. Alkalinity of tubule cells seems to favor the tubular secretion of K and a high K content of these cells seems to favor alkalinity of the urine. This suggests that the K is secreted into the urine as KOH or as K in exchange for H. In this connection the papers of Pitts and of Berlincr are particularly valuable.

2. *Hormones.* Adrenaline causes an initial rise in plasma K followed by a fall.[25] K is first apparently liberated from the liver along with glycogenolysis (the adrenal-hepatic function) but its distribution to muscles is facilitated by adrenaline and this accounts for the secondary fall in plasma K. Hormones of the adrenal cortex lower plasma K partly because they facilitate the excretion of K by the kidney. There is good evidence that they also facilitate the movement of K into cells although we have looked in vain for such an effect in isolated muscles. Pitressin and thyroid raise the plasma K concentration.[22] Insulin lowers K, presumably through its effect on the sugar.

3. *Drugs.* Plasma K is increased by histamine, acetylcholine, nicotine and tyramine and it is decreased by anesthetics. K is liberated by muscles by acetylcholine only at the threshold of contracture and presumably the liberation from nerve is of a similar nature.[23] The action of anesthetics is presumably the converse of the effect of stimulation and activity.

4. *Nerve stimulation.* K is liberated into the blood stream not only by motor nerves and the contraction of muscles but also from sympathetic nerve stimulation, the splanchnic nerve, the vagus nerve below the heart, the vagus nerve to the heart, the hepatic nerves, and oddly enough, the central end of the sciatic (with or without adrenals present).[21]

5. Other miscellaneous factors might be added, not all of them perhaps clearly distinguished from factors already mentioned. Such items are hemorrhage (anoxia), dehydration, cold stress (adrenals), cholinesterase activity (Greig), rise of temperature or fever and 20 per cent CO_2.

From this extensive list of factors which influence the movements of K it is evident that the clinician who is charged with the regulation of the electrolyte balance of the body for the preservation of health is contending with an extraordinarily complicated situation where many conflicting influences contribute to confuse the explanation of the effects observed. Subsequent speakers will doubtless define more accurately these and other individual factors and outline in more detail the complications resulting from their combined actions.

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CHAIRMAN MC QUARRIE: We will have occasion to discuss the various aspects of Dr. Fenn's paper later, hence we will not disturb him with questions now but will continue the program with Dr. Mudge's presentation which fits right into the picture.

Cellular Mechanisms of Potassium Metabolism

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Columbia University, New York City

THE PROBLEM of the cellular accumulation and transport of K was considered from the point of view of the cell constituents and chemical reactions which might be involved. Two tissues from the rabbit were studied by *in vitro* techniques—an intact cell system of kidney cortex and a cell free suspension of liver mitochondria. Suitable modifications of standard procedures of enzyme chemistry were employed. Tissue slices or homogenates were incubated in Warburg vessels with measurements of oxygen consumption and subsequent determination of electrolyte content by direct analysis immediately after incubation. Dynamic aspects were examined by the use of radioactive isotopes.

Kidney slices, prepared in cold isotonic NaCl, rapidly lose K. The reaccumulation of K from a low external concentration is dependent on aerobic oxidation as modified by oxygen tension, temperature, or the addition of suitable substrate. All inhibitors which depress respiration, cyanide for example, also prevent K accumulation, while some compounds inhibit K uptake at concentrations significantly less than those required for depression of oxygen consumption. Inhibitors of carbonic anhydrase and cholinesterase have no specific effect. 2, 4-dinitrophenol (DNP) and related compounds show a good correlation between depression of K uptake and uncoupling of oxidative phosphorylation.

Studies with K^{42} in the steady state show complete exchange of tissue K in about 60 minutes during aerobic incubation (figure 1). A fast and slow component can be identified. Since the fast component accounts for ten times as much K as can be attributed to a reasonable extracellular space, it follows that (1) intracellular K is nonhomogeneous, consisting of a slow and fast component and that (2) the exchange of most of the tissue K is not limited by a restraint at the level of the cell membrane. With anaerobic incubation 45 per cent of the K in the tissue is nonexchangeable. Since aerobic exchange is complete it follows that the exchangeability of this fraction is directly determined by

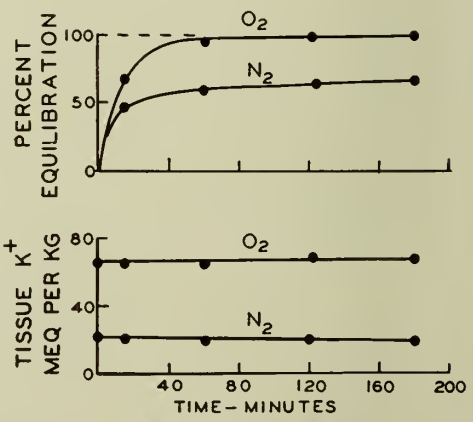

Fig. 1. *Comparison of effects of aerobic incubation on K exchange in kidney slices.* Isotopic K was tipped in at Zero time. Note complete aerobic equilibration; anaerobic experiment shows initial rapid phase, hut incomplete equilibration. By direct analysis, tissues have steady K concentration, hut aerohic tissue has about three times as much K as anaerobic.

metabolic reactions. The system is relatively stable since the effects of anaerobic incubation are completely reversible. The amount of K which is anaerobically nonexchangeable appears to be independent of the external K concentration.

Under similar conditions the rate of Na exchange is not modified significantly by metabolic reactions, nor is K exchange limited by the concentration of Na. It is concluded that the actual amount of K which moves in and out of the cell is independent of Na, although net changes reciprocate.

The action of mercurials was studied because of their pharmacological interest. Although no precise concept of their mode of action was established, the following points were documented: (1) mercury can modify tissue electrolyte composition, leading to a loss of K and a gain of Na, without inhibiting respiration; (2) the organic mercurials are effective at the cellular level in an acid, neutral, or alkaline pH; (3) they have no effect on the anaerobically nonexchangeable fraction of K; and (4) they cause

the tissues to swell markedly due to an isosmotic increase in cellular hydration.

The observation that a definite moiety of tissue K is anaerobically nonexchangeable and that all K is aerobically exchangeable suggests the interpretation that a fraction of tissue K is bound in some type of complex and may be exchanged with other K only under conditions of active aerobic metabolism. Further studies were therefore undertaken of a cell free system by Stanbury and Mudge in an attempt to obtain data pertinent to this hypothesis. The mitochondrial fraction was selected for study because of its high rate of aerobic oxidation and associated phosphorylation reactions. Direct comparison of kidney and liver, with reference to both slices and mitochondria, shows qualitative similarities; quantitative aspects are still to be defined.

Viable liver mitochondria, prepared by differential centrifugation, were washed successively with iced 0.150 M NaCl with aliquots being taken for K and N determinations. It was not possible to obtain K free suspensions and there was little change in the K/N ratio after the third or fourth wash (figure 2). Thrice washed preparations were incubated at

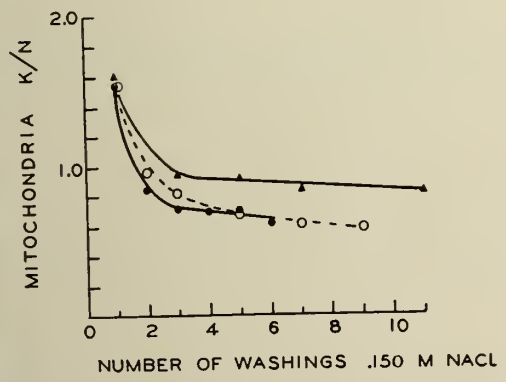

Fig. 2. *Changes in the ratio of K in mitochondria.* Mitochondria were subjected to repeated washes at 0° C. The three curves represent three separate experiments. The K/N ratio is expressed as mEq./gm.

25 degrees with α-ketoglutarate, tris buffer, $MgCl_2$, KCl and tracer amounts of radioactive isotope. After incubation the mitochondria were analyzed for K and N after they had again been washed three times with iced 0.150 M NaCl. Maintenance of the mitochondrial K concentration depends on aerobic metabolism; K was rapidly lost during anaerobic incubation or without added substrate. Almost complete equilibration of K between media and mitochondria occurred after 60 minutes incubation under optimal conditions. In mitochondria which have been labelled with K^{42} the radioactivity is the same whether subsequently washed with iced NaCl or KCl (table 1). The observations may be summarized as showing that mitochondrial K exists in a form which does not participate in simple physical exchange but which does exchange under appropriate metabolic conditions.

MITOCHONDRIA AFTER INCUBATION
washed 3 X in iced 0.15 M salt solution

	washed in NaCl			washed in KCl
Exp.	K/N	sp. act. $\frac{\text{mito.}}{\text{media}}$	K^{42} cts/mg N	K^{42} cts/mg N
1	1.02	0.82	136	104
2	0.81	0.71	152	154

Table 1. *The incorporation of K^{42} into liver mitochondria.* Paired 2 ml. aliquots of mitochondria were incubated with α-ketoglutarate in oxygen at 25° C. for 60 minutes. After incuhation one sample was washed in NaCl, the other in KCl. The harvested mitochondria contained 8 to 10 mEq. K; the total wash fluid contained approximately 34,000 mEq. Na or K. Note that during incuhation mitochondrial K has exchanged with medium K, but that during the washing procedure (without substrate and in the cold) there is no exchange between mitochondrial and medium K.

Potassium binding and exchange are inhibited by Hg and Ca; inhibition by the latter can be completely reversed by Mg. Extremes of pH and high osmotic pressure are also inhibitory. Increasing amounts of orthophosphate progressively stimulate oxygen consumption and decrease K binding and exchange; comparable respiratory stimulation from AMP has no effect on K.

In mitochondrial preparations an attempt has been made to correlate K exchange and P metabolism. Observations with DNP have been most productive and have revealed a previously undescribed polyphasic action of this drug. Concentrations of DNP (10^{-4}M), which are known to uncouple phosphorylation from oxidation in this system, inhibit K binding and exchange and liberate orthophosphate from the mitochondria to the medium. On the other hand, an increase in the concentration of DNP to 10^{-3} M stimulates respiration, leads to the disappearance of orthophosphate from the medium and permits increased exchange with medium K. These effects of high DNP concentrations are seen when α-ketoglutarate (or one of its immediate precursors, citrate, glutamate, or proline) is used as substrate and they appear to be associated with the formation of a phosphorylated substrate. (Stanbury and Mudge, in preparation). The data suggest that in the course of aerobic oxidation certain mitochondria-P-K complexes are formed, the breakdown and resynthesis of which are responsible under these conditions for K exchange in the mitochondria.

Although the experimental data can be interpreted in terms of a pumplike mechanism for K, such a physiological role remains hypothetical and other interpretations are possible. No attempt should be made to extrapolate from the present observations to any comprehensive scheme of cellular K metabolism.

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DISCUSSION

DR. MC QUARRIE: . . . I should like to ask Dr. Fenn if it is possible for him to fit the interesting role of mitochondria discussed by Dr. Mudge into his scheme and make the interpretation a little clearer for us.

DR. FENN: I can't fit it in, of course, because there isn't supposed to be any bound K, but that doesn't mean I think it is wrong. It is a fine story and I found it exceedingly interesting and have no doubt it is true.

I do recall one paper by E. J. Harris (J. Physiol. 117: 278, 1952) in which he found that 20 per cent of the K in muscle was nonexchangeable at 0° C. Do you suppose, Dr. Mudge, that is the same fraction with which you are dealing?

I should like to ask also whether this fraction, which is bound to the mitochondria, accounts for all the nonexchangeable anaerobic K which you have found?

. . . I gather that K goes out more rapidly than other substances. Does it go out more rapidly than an equal amount of Na?

DR. LARDY: I should like to offer my congratulations for this very fine piece of work, or many pieces of work, that Dr. Mudge has presented.

We certainly agree that there is bound K in the mitochondria. Miss Berger, who is here, has been studying that and has found bound K in sucrose-prepared mitochandria which is not exchanged under ordinary conditions with other electrolytes but which can be displaced from the mitochondria when they are treated with substances like dinitrophenol (DNP). I should like to ask about the unusual phenomena concerning the biphasic or triphasic responses to increasing levels of dinitrophenol. If I am correct, you did this with liver mitochondria. We have done similar experiments for another purpose in which the concentration of dinitrophenol was varied and, in the presence of ATP, we get a perfectly linear increase in respiration with increasing concentration of DNP. You do have some ATP present, I believe. Since these results are different from those reported by Dr. Mudge, I am going to predict that the differences hinge on the presence of varying amounts of microsomal material in the liver mitochondrial preparations. Mitochondria prepared in sucrose alone, are relatively free of microsomes while those made in solutions containing electrolytes contain appreciable amounts of microsomes. Perhaps looking into that aspect of the problem will iron out the differences between the two laboratories.

DR. MUDGE: I am sorry that I am not familiar with the recent experiments of Harris. Several years ago Wesson, Cohn and Brues demonstrated a similar nonhomogeneity in the K of muscle in tissue cultures.

As to the amount of K on the mitochondria, the fraction for liver is about 2 per cent of the total cell K. The anaerobically nonexchangeable fraction of kidney is 8 milliequivalents per kilo; and normally there are 70 milliequivalents in the kidney so that would account for 10 or 12 per cent. The question, of course, is, "Does mitochondria K account for all the nonexchangeable K in kidney." We cannot answer this as yet, but I think that we may reasonably expect quantitative differences between various cell types.

As to Dr. Lardy's question, I think probably the reason for different results is that we are using slightly different systems. Although a number of variables remain to be explored, I suspect that the concentrations of phosphate and adenylic acid are of major importance.

The Distribution Kinetics of Intravenous Potassium K^{42}

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WHEN potassium, K^{42}, is injected quickly into the circulation of rats,[1] the isotope disappears from the blood plasma in four to five exponential stages of significantly different rate (figure 1). Separate curves for tissue uptake indicate what organ pools of potassium are mainly accountable for the plasma stages. We have fitted the data to the equation of Sheppard and Householder[2] for a mamillary system in which the common carrier, the blood plasma, acts as a central pool to shuttle tag back and forth between the various peripheral tissue pools, according to their exchange rates.

The first *disappearance* stage 1 is truly a transcapillary transfer. Its rate is so fast that earlier workers[3] overlooked it. In order to delineate it, we[4] had to bleed rabbits, after an ear vein injection of K^{42}, almost continuously from the carotid artery by means of polyethylene tubing to effect rapid-fire sampling (figure 2). This led to such early samples that we began to detect the circulatory mixing wave which was later to be accurately delineated for K^{42} in the dog by Sheppard, Overman, Wilde and Sangren.[5] Overman and Davis[6] later showed, as Sheppard et al. had surmised, that the circulatory mixing wave for T1824 compeltely overlies the early mixing wave for K^{42}, which latter is thus shown likewise to measure cardiac output by the indicator injection method.

Walker and Wilde,[4] noting in stage 1 that 90 per cent of the injected tag left the circulation in one minute, were surprised that the ordinate intercept of the log plot for this stage resembled that expected had the full dose of K^{42} been dissolved initially in the plasma volume (figure 2). Since plasma K^{42} was almost compeltely cleared from the plasma after three circuits around the circulation, it was obvious that a marked gradient existed along the capillaries and that the tag could not possibly be disappearing from a well-mixed plasma pool such as that implied by the value of the ordinate inter-

*Research Participant, Oak Ridge Institute of Nuclear Studies.

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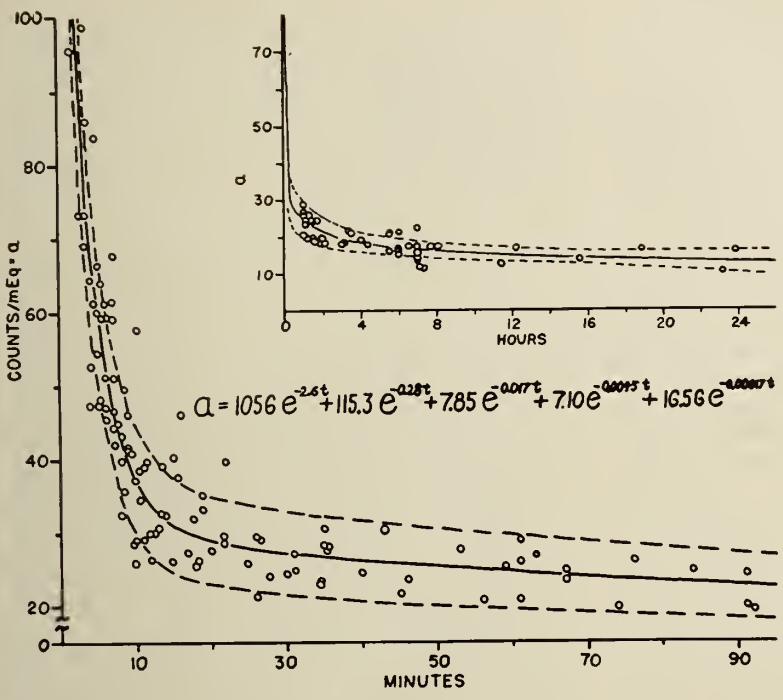

Fig. 1. Complete time course of plasma specific activity. *a*. Composite curve for many rats. Broken lines are drawn at a distance equal to two *standard errors*, S.E., away from the continuous line which was fitted by least squares. The S.E. values are derived for means rather than for individual values within each time array. Note that the time unit for the insert is in hours.

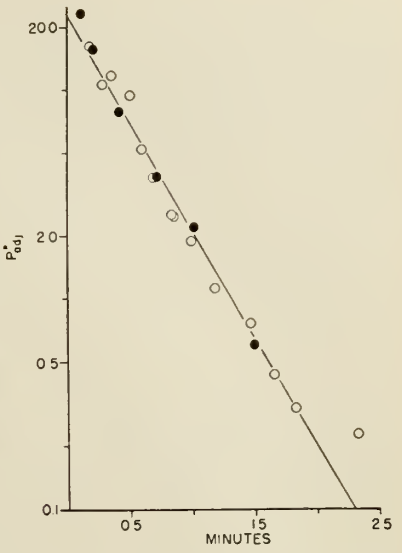

Fig. 2. The effect of chemical K dosage on the initial or transcapillary transfer of K^{42} out of the circulating plasma. Ordinate is radioactivity counts per ml. plasma divided hy counts injected per gram of rabbit body weight, expressed on logarithmic scale. *Open circles* (○): a 3.3 kg. rabbit received 0.29 mEq. K in 324 mEq./liter solution; calculated increment of concentration in assumed plasma volume, + 2.24 mEq./liter. *Solid circles* (●): a 3.5 kg. rabbit received 0.003 mEq. K in 3.0 mEq./liter solution; calculated plasma elevation nil.

cept. Sheppard et al.[5] showed, by a new mathematical approach, that the intercept would nevertheless predict plasma volume provided that the combined circulatory mixing and disappearance occur without appreciable time delay nor loss of tag between injection and sampling sites.

Since K movement was faster than that of other electrolytes, by an amount exceeding that expected because of its smaller hydrated ion radius (lyotropic series), we investigated whether certain organs such as the liver have a special property to take up plasma K and thus accelerate the decline of plasma K^{42}. Fenn et al.[7,8] found evidence for a mass movement of K into the liver when plasma concentrations were markedly elevated. Such elevation was unavoidable in their hands since they worked with cyclotron material of lower specific activity. It was also unavoidable in our early work performed in New Orleans at a distance from the Oak Ridge reactor. More recently, however, we have used the facilities of the Oak Ridge National Laboratory Biology Division at Oak Ridge and, for the first time, have been able to inject truly traceable amounts of K. The slopes of the curves are identical to those with the largest chemical doses which, from the standpoint of toxicity, are safely imposable (figure 2). For that matter, complete evisceration, including removal of the liver, leaves the rate of disappearance unchanged.

In the rabbit, it appears that the fraction of circulating K^{42} removed from the circulation per minute is numerically equal to the fraction of the plasma volume pumped through the heart. This precludes the possibility that the precipitous decline of K^{42} is explained by uptake by certain rapidly exchanging organs such as the liver, for this accomplishment would require a blood flow to the liver equal to the cardiac output. The fast rate of transfer is a property common to all capillaries and stage 1 is truly a transcapillary event.

Re-examination of earlier curves[9] based upon chemical K analyses after massive potassium injections reveals the same fast initial rate. This may be useful information concerning what is a safe rate for injecting the relatively toxic K as therapy for K-deficient patients. (See Discussion following Dr. Butler's paper.)

Stage 2 in the rat[1] extends through 20 minutes. As early as 5 minutes the kidney specific activity has reached a peak which exceeds the plasma by threefold. Thus during the remainder of stage 2 the kidney is donating this enriched tag to other organs. At about 10 minutes the intestine has equilibrated with the plasma. During the midcourse of stage 2, kidney and gut are shuttling tag to liver, skin, muscle, and other even slower organs. Hours later the cumulative urine K^{42} is only a third of the total K^{42} present in the two kidneys at 5 minutes.

Stages 3 and 4, not so widely different in rate from each other as other adjacent stages, represent movements of tag from plasma, kidney, intestine, liver, and skin, as lumped pools, into muscle, etc. Stage 5 represents some movement into brain and

into erythrocytes but also includes the so-called "'biologic decay" or wash out of tag from the body into urine and feces, etc.

The measurement of the total exchangeable mass of body K has attracted the attention of several groups of workers.[10,11] Three of our rats, when digested in warm nitric acid, yielded flame photometer values of 78.6 mEq. of K/kg. Other rats of the same age and stock (Sprague-Dawley), using isotope dilution technique, were estimated to contain 60.6 mEq. of K/kg. at 7 hours and 77.2 mEq. of K/kg. at 24 hours. These figures are uncorrected for K^{42} loss to the urine amounting to 5 per cent of dose. Possibly the corpuscles, and certainly the brain, had not yet received their share of tag. In another experiment involving analyses of individual organs, certain organ values when added contained 90.4 per cent of total body potassium and 88.7 per cent of the K^{42} dose. Several organs, including muscle, undergo complete exchange of all their K as judged by the fact that their specific activities do not differ significantly by statistical test from plasma at 7 hours.

* * *

It is a pleasure to acknowledge mathematical and statistical aid from Drs. C. W. Sheppard, A. W. Kimball, J. Z. Hearon, and Mr. G. J. Atta.

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DISCUSSION

DR. BURROWS: I should like to compliment the authors of this painstaking work. I think it is important for those of us who are trying to do isotope dilution studies to ask Dr. Wilde if he thinks this heterogeneity of tissues in respect to the distribution of K^{42} persists very long? He has shown us quite a difference between different tissues in the first few hours. We like to think the tissue distribution of K^{42} in human subjects is pretty complete and pretty homogeneous at the end of probably 18 or 20 hours. We would like to have him comment on this.

DR. FENN: I gather that K goes out more rapidly than other substances. Does it go out more rapidly than an equal amount of Na?

DR. WEIL: I was wondering whether the exchange of bone has been taken into consideration?

DR. BRUHL: I would like to know if the K^{42} is only accumulated in the kidney or is it excreted at the same time in the urine.

DR. MC QUARRIE: I am concerned about the brain. Can you get more K in the brain quicker if it is injected? Have you done that with dogs? Have you determined the spinal fluid content?

DR. WILDE: As to the problem of measuring exchangeable K mass by isotope dilution as conditioned by the adequacy of mixing, note that nine hours after injection into the rat the tag is uniformly mixed in the organs listed in the last chart—namely, kidney, intestine, liver, skin and muscle. The brain and erythrocytes are much slower but you see these first named organs comprise 75 per cent of the body K in which the tag is completely mixed at nine hours. Incidentally, in the rat, urine collected after 40 minutes will mirror plasma specific activities very accurately and so can be used for calculating exchangeable mass at any later time whenever tissues and plasma are considered to be equilibriated.

As to Dr. Fenn's question concerning the relative rate of loss of K^{42} and Na^{24} from the plasma, in Morel's work (Helvet, Physiol. et Pharmacol. Acta 8:52), Na^{24} in his rabbits is about four times as slow as K in our rabbits. I might say briefly that of the different ions which have been measured in this fashion—various *anions,* chloride and sulfate, have equal rates of loss from the plasma. These anions collectively are equal to the *cation* sodium (Sheatz and Wilde: Am. J. Physiol. 162: 687:1950) which as stated is four times slower than K. The work to date (Flexner et al.: J. Biol. Chem. 144:35: 1942) on the disappearance rate of heavy water, D_2O, has required such large samples of plasma that only infrequent samples could be taken. This does not allow adequate analysis of the earliest transcapillary rate. Judging from the data available D_2O is faster than Na but slower than K.

We have not studied bone.

In considering the manner in which the kidney handles the K^{42} presented to it, suppose that the amount of K^{42} accumulated in the two kidneys during the first two minutes be expressed as a renal plasma clearance. This amounts to 20 ml. of plasma per minute. This is a reasonable value for the entire renal plasma flow. It indicates that tag is presented to the kidney by secretion, a movement from the peritubular capillaries into the tubular epithelium, as well as by filtration followed by reabsorption. The latter process is not fast enough to account for the rate at which tag accumulates in the renal substance. At two minutes the kidneys contain at least three times as much tag as will appear as an accumulation in the urine even hours later. It is obvious that tag is migrating into and out of the renal substance at a rapid rate irrespective of the net movements required for the transport of K to the urine.

Concerning the question of the slow rate of entry of tag into brain, it is to be noted that Krebs et al. (Biochem. J. 48:530:1951) find a faster rate of turnover of K in brain slices than is to be inferred from our data. Also Greenberg et al. (Am. J. Physiol. 140:47:1943) find that K^{42} enters *new-formed* cerebrospinal fluid rather promptly. This refers to K^{42} collected from a freely draining cisterna magna. It is possible that in a closed CSF system, with higher pressure, the tag enters more slowly or that mechanical mixing by flow within the fluid is slow, such as to give us our slow rate *in vivo.* We have not attempted to analyze spinal fluid in a rat.

DR. GINSBURG: (A comment with respect to the kidney.) The rapid uptake of K^{42} by the kidney may in part be due to a stimulation of the renal secretory mechanism by the increased K load. The actual dose we gave the rats would amount to about 60 per cent of the total plasma K. Even though the disappearance from the plasma is extremely rapid this might represent, for a brief period immediately after the injection, a K load capable of stimulating secretion of K in the kidney. This,

possibly combined with a lag time for tubular travel, might account for the high level of activity in the kidney present a few minutes after the injection.

DR. MC QUARRIE: I should like to ask you, Dr. Wilde, if you have given some thought to carbohydrate or glucose and if that would make a difference in the liver or elsewhere. Do you know whether that does influence this?

DR. WILDE: In an attempt to relate liver uptake of K^{42} to glucose movements, we tested the effects of injecting glucose or insulin ahead of the K^{42}. We were unable to show changes but, of course, it is possible that our glucose or insulin injections were inappropriately related in time to the K^{42} injections.

The Role of Potassium in the Activity of Nerve Cells

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One physiologically significant process that occurs within a nerve cell is the conduction of the nerve impulse. This coordinated sequence of physical and chemical events is characterized by changes in the potential difference across the cell surface and the consequent flow of electrical current. These action currents provide an adequate stimulus to adjacent regions of the cell, and thus the wave of electrochemical change spreads from one end of the neuron to the other. In the total cycle of events associated with the conduction of a single impulse there are many processes that may be described generally as (1) structural changes, measured in terms of changes in ion permeability or membrane impedance; (2) ion transport, reflected in measured electrical currents; and (3) metabolic events, measured by oxygen uptake, or CO_2 output. This neuronal activity has been systematically studied by electrical, by electrochemical and by chemical methods.

In the electrochemical studies of nerve activity attention is focused upon the transport and average spatial distributions of specific ions. These studies have revealed that the concentration of K ion is high inside a nerve cell relative to the concentration in extracellular fluids. The reverse is true for Na ion.[1] Almost all interpretations of the electrical properties of neurons at rest and during activity are in terms of electrochemical processes involving transport of these two ions[2,3,4]. The oxidative metabolism is brought into this picture to provide the energy required to maintain or restore the Na and K ion distributions.[3,4,5] This energy is required because (1) it is known that the nerve membrane is permeable to both of these ions and (2) the observed concentration differences are far from those of thermodynamic equilibrium. There is, at present, no general agreement on the physical mechanisms involved in this utilization of chemical energy to produce the neuronal electromotive force. Recent evidence has given the K ion a direct role in the action current and thus in the mechanism of conduction of the nerve impulse. The principal facts are: (1) K leaks out of an axon during an action current and Na leaks in;[6] (2) the inward leakage of Na decreases the membrane potential and even reverses it in Squid axons, accounting for the rising phase of the action potential;[3,7] (3) the membrane potential returns to its original level by outward movement of K ions, accounting for the falling phase of the action potential.[3,7] Analysis of the major facts has led Hodgkin to the view that the outward leakage of K begins more slowly than does the inward movement of Na ion.[7] Hence the exchange of charged particles is not balanced at all times, and the potential difference across the membrane changes.

What is the physical meaning, in terms of changes of membrane structure, of the concept of a sudden change in sodium ion permeability followed by a slower change in K ion permeability? In answer to this question Nachmansohn has developed the idea that acetylcholine released by an adequate stimulus acts upon a structural protein of the membrane to change the permeability to Na. This involves the acetylcholine system and choline acetylase and thus suggests one more possible point of action for K.[8]

A far older hypothesis also places K ion as the main electroactive unit in determining the potential difference across the membrane of resting nerves.[2,3] According to this theory the difference in concentration of K ion between the inside and outside of an axon forms a concentration cell with the observed electromotive force. The concentration difference was considered to be about right to account for the rather inaccurately known potential difference. Furthermore, the potential changed with the outside concentration of K ion approximately as required by theory. However, with the advent of the more precise methods of measuring membrane potentials and with more attention to the changes at the low concentrations of outside K there have been observed significant discrepancies (cf. [3,4] for references).

Recent experiments on permeability to ions have focused attention more sharply than ever before upon the fact that Na and K can pass through the membrane.[3,6,4] Therefore, it is a prevailing view that the observed concentration differences must arise by a process requiring a continuous expenditure of energy. One of the suggested mechanisms is that some process continually extrudes Na ions against the observed concentrations gradient.[3,5] In contrast to this hypothesis Shanes interprets his accumulated evidence to mean that the K ion is

transported into the cell by some metabolic process.[4]

Regardless of the detailed mechanism the distribution of ions begins to change toward an equilibrium state if oxygen uptake is prevented. It has been established that K leaks out of the anoxic nerve and is reabsorbed when oxygen is again supplied.[4] Furthermore, the potential difference across the membrane requires continued oxidation for its maintenance.[9,4] These facts direct attention to the relation of oxidative metabolism to the maintenance of the electrochemical properties of nerve and the capacity to conduct impulses.

The rate of oxygen uptake of nerve cells changes markedly when the K ion content of the bathing solution is increased.[10,11] This metabolic effect is reversible and is related to the concentration. When the K ion concentration bathing a frog nerve is changed to about 40 mM (20 x Ringer's proportion) the rate of oxygen uptake slowly increases to reach a maximum at about 40 minutes and then declines. The final steady rate is lower than that for the nerve in Ringer's solution. If the change in K ion concentration is not so great the increase is more gradual, reaches a lower maximum value and declines very slowly. Thus at 20 mM the rate of oxygen uptake may be above normal for three hours.

If attention is confined to effects produced in about one hour then the rate of oxygen uptake of nerve cells is always increased by increase in K concentration. Furthermore, in frog nerve with perineurium removed it was observed[10] that a maximum increase in rate of oxygen uptake occurred between 20 and 30 millimolar KCl. Approximately the same relation to concentration was observed in crab nerve by Shanes and Hopkins (cf. [3] for reference). It is significant that a similar dependence of rate of oxygen uptake on external K ion concentration has been observed for muscle.[12] This effect of K ion on oxygen uptake of nerve and muscle cells varies with concentration as does the action of K ion on the activity of enzymes concerned in phosphate transfer to adenylic acid.[14]

It is pertinent to inquire whether these actions of excess K ion upon metabolism are directly correlated with action upon electrochemical properties of nerves. At the time that conduction block occurs the rate of oxygen uptake is actually increased. However, the depolarizing action is a slow process,[9] and at the time that it is essentially completed the rate of oxygen uptake is depressed as first observed by Chang, Gerard and Holmes (cf. [4] for reference). It is also possible that K ion may be a link between conduction of an impulse and oxygen metabolism. This suggestion is based upon three facts: (1) conduction of the impulse is associated with leakage of K ion; (2) increase in K ion concentration outside of a nerve initially produces increased rate of oxygen uptake; (3) following an impulse there is an increase in oxygen uptake.

In conclusion the action of increases in K ion in initiating action potentials should be mentioned.[13] The initial effect upon excitability is an increase which is followed by a steady state of depression. If this transient decrease in threshold for excitation is sufficient a train of impulses will be initiated from the chemically modified area of the cell. This excitatory action is always transient and is followed by a steady state of raised threshold. At the higher concentration this depression of excitability is sufficient, together with the depolarization, to block conduction. These actions of K ion are very rapid compared to the action upon oxygen uptake.

Potassium ions have entered into the studies of the properties of nerve cells at every phase of the investigations. The potential difference across the membrane, the flow of action currents, the excitability, the rate of oxygen uptake are all modified by the concentrations of K ion to which the cell is exposed. This circumstance suggests looking for causal relations. For example, it is possible that the action of K ion on the rate of oxidative phosphorylation may be the cause of changes in rate of oxygen uptake in neurons. Its action upon rate of phosphate transfer may influence the utilization of adenosine triphosphate in ion transport and thus change the membrane potential. Perhaps the action of K ion upon some enzyme of the acetylcholine system is connected with the changes in excitability in a neuron exposed to excess K. All these connections are possible since one necessary condition has been established—these processes are sensitive to changes in K ion (and Na ion has opposite effects or no effect at all in each instance). However, it is equally apparent that our present information is not sufficient to permit a selection of one system of such causal relations as being preferable to another. It is remarkable that the ions that act like K in depolarizing axons (NH^+, RB^+)[2] are those which act like K in its action on phosphate transfer and on oxidative phosphorylation.[15] However, this is a necessary but not a sufficient condition for a relation between these particular chemical reactions and the electrical properties of the nerve.

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DISCUSSION

DR. MC QUARRIE: The amount of physics in Dr. Brink's paper confirms what Dr. Fenn said about the place of

physics in neurophysiological problems, and so we will ask him to comment on these concepts.

DR. FENN: I am interested in the increased oxygen which goes along with nerve impulse and I should like to ask whether you think it is possible to have a nerve conducting impulses without any measurable increase in the oxygen consumption.

I also found many years ago that the amount of oxygen per impulse was less at higher frequency. In the first place, that might be due to failure of the nerve to respond to every shock at high frequencies. Perhaps, also, the nerve impulses were subnormal in size at the higher frequencies.

DR. BRINK: The first question was whether or not a nerve can conduct impulses without an increase in the amount of oxygen used. The A-fibers of a frog's sciatic nerve can conduct impulses at 50 per second for long periods of time without the usual increase in rate of oxygen uptake. This was discovered some years ago in the course of some studies of the action of sodium azide upon nerve metabolism. At a concentration of about 10^{-4} mols per liter, the capacity for conducting impulses seems unimpaired for at least 24 hours and the nerves can conduct as many as a million volleys of impulses without increasing the rate of oxygen uptake above that measured in the resting nerve. This observation has been confirmed in Dr. Gerard's laboratory, using different experimental methods. At present there is no question about this fact. However, it is not known to what extent this change in oxygen utilization is reflected in the heat production of these modified nerves.

According to the Na hypothesis for the action potential, the immediate source of energy for conduction of nerve impulses is the difference in Na concentration between the outside and inside of a nerve cell (Hodgkin). During each impulse some Na leaks in and some K leaks out. Energy is required to re-establish the initial ion distributions. It is usually assumed that the extra oxygen uptake of active nerve represents the utilization of oxidative chemical energy for this purpose. There is no direct experimental evidence for this assumption. However, if this assumption is correct and, if the Na hypothesis is correct, then a nerve treated with 0.1 mM sodium azide should accumulate a small amount of Na each time it conducts a volley of impulses. This expectation has not been adequately tested. One would also expect that the action potential would become smaller as the Na concentration inside the nerve increased. This is also under investigation in azided nerves but has not been adequately tested. It is obvious that the apparent lack of effect of 0.1 mM sodium azide upon conduction could be explained by the above ideas.

It was suggested that the amount of ionic exchange may be greater for impulses at the beginning of a train than for those occurring later and that this might explain the fact that the extra oxygen used per volley is greater initially. Such an explanation will have to be considered if it is shown experimentally that ion exchanges per volley are functions of frequency of impulses and of duration of the train, as the quantities of oxygen per volley are known to be (cf. Symposium on Quantitative Biology, Cold Spring Harbor, 1952).

DR. LARDY: Dr. Fenn introduced an interesting concept in the differences of energy required to maintain various gradients by an ion pump. What is the nature of this pump? Is it on a fluid basis or does it operate like a bucket brigade where one mole of high energy phosphate would be required to move one mole of K? Under the latter circumstances, it would take the same amount of energy per unit quantity of K transferred regardless of the nature of the gradient, whereas on a fluid basis, it should take less energy per unit of K when the gradient isn't so steep.

DR. BRINK: The amount of energy *used* to transfer ions across axon membranes is not known. The work *required* has been estimated but these estimates do not involve mechanism of transfer.

The Absorption and Excretion of Potassium in the Intestine

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THE ROLE of the intestine in the body economy of potassium is an important one because (1) the digestive secretions contain considerable amounts of that ion, (2) the intestinal wall is rather freely permeable to it, and (3) absorption of dietary K is crucial to balance maintenance. For reasons which are not obvious relatively little attention has been paid to the intimate details of the mechanism of K transport in the gut. In fact, a search of the literature in connection with this topic has shown as the most noteworthy result the paucity of information about the subject. It is generally stated on rather slight evidence that the absorption of the Na and K salts of various anions is not greatly different. With regard to the mechanism of absorption of K ion and the influence of various agents upon it, almost nothing is known with certainty.

Dennis and Wood[1] studied the absorption of Na, K and chloride from isotonic solutions of the following compositions: (1) KCl 13.4 mM/1, NaCl 142.6 mM/1, (2) KCl 13.4 mM/1, NaCl 78.7 mM/1, $MgSO_4$ 104 mM/1. They employed dogs before and after adrenalectomy provided with surgically prepared Thiry-Vella loops excised from the lower 40 cm. of the ileum and arranged with fistulae at each end tunneled through the abdominal wall. The results showed that adrenalectomy decreases the absorption rate of both Na and K but the effect on K is considerably less marked than that upon Na. The most striking effect on intestinal absorption of adrenalectomy and deprivation of therapy is the failure of the intestine to absorb water. There is coincidentally a decrease in the ability of the intestinal epithelium to lower the total osmotic pressure of initially isotonic solutions placed in the gut.

Experiments using radioactive K made by Grim and Lee[2] show that the specific activity of K in intestinal lymph is higher than that in venous blood from a loop of intestine containing such K in low concentration. There is an indication that this cation

is absorbed initially into the interstitial fluid and lymph and passes subsequently into the blood. Since the same analytical findings are observed with Na there is no indication of a specificity in route of absorption. It is of interest, however, that when H_2O is labeled with D_2O the concentration of the latter in intestinal lymph from a loop filled with the tracer in appropriate dilution, is less than that found in the corresponding venous blood. There is, therefore, an indication that with respect to water the lymph may equilibrate partially or completely with blood which has not passed through the intestinal epithelium, whereas the cations above mentioned may not permeate rapidly enough in relation to the rate of movement of the lymph to accomplish this equilibration. Other interpretations of the findings are possible but appear to be less likely.

Potassium moves freely across the intestinal epithelium and without doubt when there is a net loss of H_2O into the intestine K can be lost to the body with it. Therefore, in any condition in which there is excessive H_2O loss in the stool K loss can be anticipated. The studies of Dennis and Wood indicate that in adrenal insufficiency the Na loss might be relatively greater than the K loss. In other situations the reverse might be true.

The major factor in salt loss from the body via the intestine is the motility of the gut and the time for absorption in the ileum and colon. It has been demonstrated for H_2O, Na and chloride that the duodenum and jejunum are poor absorbers because the rates of movement of those substances across the epithelium in both directions are high and about equal. Therefore net transport is zero. In the ilium the rates are smaller but deviate so that net movement is appreciable. In the colon the transport rates are very low but under proper circumstances may differ widely so that the net transport becomes large. It is probable that potassium behaves similarly.

Rapid movement of intestinal content through ileum and colon is unfavorable to absorption. Stool analysis in diarrheal states shows that when K intake is high the $(Na^+)/(K^+)$ ratio in the stool may be much smaller than the ratio in plasma, indicating either a specific defect in K absorption or, more likely, inadequate time for absorptive processes to occur.

The newly developed techniques for immobilizing cations in the intestine through the use of *exchange resins* presents the organism with a new problem in connection with ionic balance. The exchange resins of the cationic type fix all metallic cations to variable extents. As Black and Milne,[3] among others, have shown, it is possible to produce K depletion in man by the administration of Na resin in large amount. It has been shown by Gregor[4] and others that resins can be produced which have relatively great specificities for the various cations. By altering the structure of the resin its selectivity can be adjusted so that relatively more or less of Na or K will be bound by it. In the clinical use of ion exchange resins their physicochemical characteristics must be recognized and when relatively non-selective materials are used, supplements of ions which would otherwise be lost to the body in excessive amounts must be provided.

In general, it can be said that the more intimate details of the mechanism of movement of ions and H_2O across the intestinal epithelium are still quite obscure. Information, particularly as to the factors which govern the rates of movement in both directions across the intestine, will be essential before it will be possible to understand the mechanism of diarrheal states. One obvious factor of importance which does not have to do with the rates of permeation is the time factor as determined by the motility of the intestine. Obviously, absorption which requires time for its accomplishment cannot be carried to completion in the absence of adequate time. Therefore, from a practical viewpoint, the control of intestinal motility may be at least as important as the control of water and ion movements.

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The Significance of Potassium in Protein Synthesis and Some Aspects of Its Interrelationship with Sodium

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The lesions of myocardial necrosis which develop in the growing rat as a result of K depletion are supposed to indicate the essentiality of this cation for actively functioning cardiac muscle. These lesions, when produced in protein-depelted adult rats undergoing protein repletion by the feeding of diets lacking K but relatively high in Na, often cause death from congestive heart failure and pulmonary edema. They do not develop, or develop only minimally, if both K and Na are omitted from the repletion ration. This raises the question whether the necrosis is due solely to a deficiency of K, or whether it may be the consequence of an ionic shift or disequilibrium whereby sodium ions replace intracellular K ions and exert a toxic effect.

Evidence of the toxic potentiality of NaCl in relation to K depletion is seen in the following experiment. Protein-depleted rats were subjected to pro-

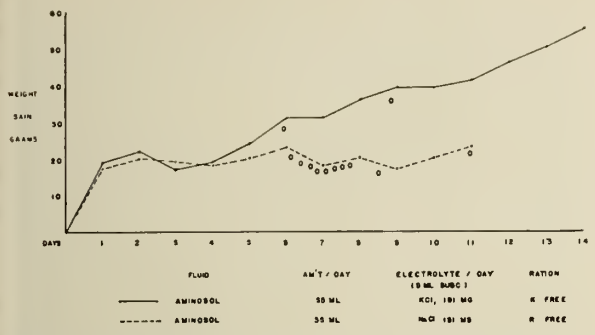

Fig. 1. The toxic action of NaCl in relation to developing K deficiency. Shown are the averaged weight changes in the course of protein repletion as described in the second paragraph.

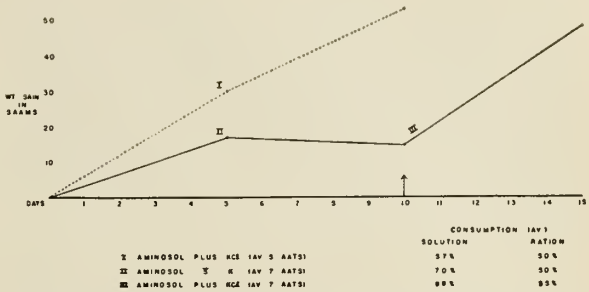

Fig. 2. Potassium supplementation of protein hydrosolates in relation to repletion of protein-depleted rats. This chart demonstrates the essentiality of K for tissue protein synthesis in repletion of protein-dietary rats fed Aminosol (Ahhott and Company) as the sole source of dietary nitrogen. The manufacturers are now adding K to this hydrolysate to correct its K deficiency.

tein repletion by means of a ration devoid of K salts, coupled with equimolar replacement by Na salts. Twenty animals were divided equally in two groups and all were given daily subcutaneous injections of a solution of either KCl or NaCl (191 mg./5 ml.). This represents the daily amount of K salt consumed in the usual repletion ration. Over a repletion period of 14 days the rats receiving KCl solution made effective recoveries, except for 2 animals which died, presumably from K overdosage. In contrast, all of the rats receiving NaCl solution, after having made brief weight gains for six days, died suddenly (8 on the sixth and seventh days and the remaining 2 by the eleventh day). In short, after only six days of a developing K deficiency, NaCl had suddenly become lethally toxic, coupled with signs of congestive heart failure and pulmonary edema. Other experiments have consistently indicated a similar determinative influence of NaCl upon the course of a developing K deficiency, whether the salt is given parenterally or orally.

The cardiac lesions elicited by a high Na intake in the course of K depletion differ from those usually regarded as indicative of K deficiency. The latter are characterized by a loss of muscle fiber substance and a conspicuous cellular replacement, often alluded to as "fibrosis." On the other hand the lesions which appear in rats undergoing K depletion and then subjected to a high Na intake are devoid of cellular infiltrates or evidence of cellular proliferation. They consist instead of extensive areas of hyaline or coagulative necrosis of muscle fibers, with swelling loss of myofibrillae and nuclear pyknosis. The lesions may be focal or diffuse, but they tend to appear subendocardially in the areas in which the so-called K deficiency lesions ordinarily appear and are presumably earlier and exaggerated manifestations of the myocardial necrosis associated with K depletion. Nonetheless it is obvious that in a consideration of the pathologic aspects of K deficiency attention must also be given to the reciprocal relationship of Na to K in cellular metabolism.

There is accumulating biochemical evidence of such a reciprocal relationship, in muscle cells in particular, and that as a consequence of K depletion the concentration of Na increases both in heart and skeletal muscle, coupled with an increase in intracellular H_2O.[1] Moreover, after K has been restored to the diet, Na is slowly extruded.[2] Increased concentrations of Na have also been found in liver tissues[3] and in erythrocytes in animals depleted of K.

If the facts revealed by chemical methods have meaning in the intact animal an increased intake of Na in the presence of a severe K deficiency should be expected to be potentially harmful. Although the adverse consequences of an increase in intracellular Na could be manifested in various types of cells, the effect should be especially deleterious in cardiac muscle fibers in the course of development of the characteristic necrosis of K deficiency.[4,5] This has been found to be the case by others and by us.

It is not suprising that serious metabolic consequences follow such ionic shifts. For example, in the early experiments of Heppel the K-deprived rats failed to gain weight, lost appetite and were definitely sick. In dogs depleted of K by injections of DCA, Ferrebee and his associates observed that the resulting symptoms of muscular weakness were prevented by the administration of KCl. They attributed these symptoms to a shift of equilibrium between intracellular and extracellular K with a loss of the former and its replacement by Na. Fox and Baer observed a loss of K and a gain in Na in the tissues of mice in which fatal shock had been produced. Darrow reported that even with a normal concentration of serum K, alkalosis may cause the intracellular fluid of muscle to lose K and gain Na, accompanied by a concomitant increase in intracellular water. From *in vitro* studies Steinbach concluded that the interchange in muscle between Na and K is reversible provided that the muscles do not lose more than about one-half of their original K content and that the Cl content of the tissue remains about the same.

In view of this evidence of intracellular ionic shifts it is of particular interest that some enzymic reactions potentiated by K are inhibited by Na. If the current assumption is correct that K plays its most important intracellular role in conjunction with enzyme reactions regulating energy mechanisms and

the production of high-energy phosphate bonds,[6] the inhibitive action of Na might under some circumstances cause harm to cellular metabolic mechanisms. Boyer and associates have shown, for example, that in the transfer of phosphate from phosphopyruvic acid to adenylic acid, a high concentration of Na is inhibitory. Sodium has also been found to inhibit the glycolysis of mouse brain homogenates and of nervous tissues of the cotton rat.

Because the myocardial lesions appear only in the course of K depletion, and because chemical analyses have shown that such hearts have an increased Na content, the assumption seems warranted that the coagulative necrosis may be due in large measure to the toxic action of Na ions on cells which have lost a critical amount of K and are undergoing Na replacement to a degree where Na ions may seriously alter intracellular enzyme activities, thus leading to necrobiosis and early autolysis of intracellular substance. Moreover, the degree of damage of myocardial fibers by the coagulative necrosis might well induce hypotonia and congestive heart failure. For example, recent evidence presented by Freed and Friedman[7] indicates an interrelationship between K and Na with respect to blood pressure changes in rats undergoing K depletion. Rats fed diets low in K but high in Na manifested a drop in blood pressure whereas this could be prevented by the simultaneous reduction of Na intake. They postulated that in the presence of a low Na content of the diet K was retained sufficiently in the tissues to prevent the development of hypotension. Inasmuch, however, as a low intake of Na inhibits the development of severe myocardial necrosis, it is also possible that cardiac hypotonia in animals receiving a high Na diet may have influenced the development of the hypotension as well.

These facts and assumptions suggest the importance, as recently emphasized by Danowski[8] in those clinical situations in which K depletion assumes pathologic significance, of attempting to control the conditions which lead to an increase in the intake or retention of Na salts. Thus in severe dehydration, in the development of edema from Na retention, and in the excessive use of salt solutions in the treatment of patients with toxemias of pregnancy, eclampsia, glomerulonephritis, etc., Na may exert an increasingly toxic effect as K depletion progresses.

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CHAIRMAN RUBIN: Since the next paper also bears on this subject, we will hold the discussion of Dr. Cannon's paper until after Dr. Phillips' presentation.

The Potassium and Sodium Requirements of Certain Mammals

R. K. SHAW, M.S. AND PAUL H. PHILLIPS, Ph.D.

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The physiological functions of K and Na are so closely intertwined that to attempt to discuss the requirements of one without the other would create a very misleading impression. In the plant world it is now conceded that Na may replace up to 30 per cent of the K requirements of certain plants. A few plants such as celery, for example, must have Na or become quite unpalatable. In many instances, experiments with animals produce striking analogies to plants. A deficiency of Na cannot be met by K while a portion (about 20 per cent) of the K requirement can be met by Na provided the K deficiency is not acutely critical. While opinion of ionic balance or ratios vary between scientists it appears that within broad limits the Na:K ratio is important. Heavy ingestion of one may raise the requirement of the other. However, it appears that when the concentration of either element does not exceed 1 per cent and it is above the minimal growth requirement for each, no deleterious effects will result from variations in their respective ratios.

There is a slowly accumulating mass of data which leads to the belief that the requirements of different species for Na and K are closely similar. These requirements vary between species principally because of the type and character of the diet. Ruminants which live upon forage plants are exposed to Na:K ratios greater than 1:5. They require more NaCl per pound of body weight than the monogastric animals. In many districts the Na:K ratio may exceed 1:15. Roughages contain 1.0 to 2.0 per cent K and 0.10 to 0.20 per cent Na. Cereal grains on the other hand seldom contain over 0.40 per cent K and 0.01 per cent Na. These facts would seem to emphasize that the total K and Na intake is the important factor rather than the ratio, in practical nutrition of farm livestock and laboratory animals. However, Meyer and his coworkers have shown that the death rate of the rat is increased with an increase of Na in the ration of the K deficient rat.[1]

The rat. The dietary level of Na or K needed by the rat has been rather closely established. The Na requirement for the growing rat was established by Osborne and Mendel,[2] Miller,[3] Olson and St. John,[4] St. John[5] and Grunert and his coworkers.[6] Experimental work at Wisconsin indicates that 0.05 per cent Na in the ration meets the requirement of the rat, (tables I and II). During the period of rapid growth of the young rat following weaning the dietary K requirement was found to be 0.18 per cent during the first four weeks of the growing period and thereafter the dietary requirements were apparently met by 0.15 per cent K in the ration. The minimum Na level of 0.05 per cent is critical and should not be used with animals under stress or with rations imposing stress upon the subject. These data suggest levels for practical nutrition of 0.09 per cent of Na and 0.18 per cent K (tables I and II).

TABLE I

SODIUM REQUIREMENT OF THE RAT AS AFFECTED BY POTASSIUM

Potassium	*Sodium*	*Average Daily Gain for Six Weeks*
0.25%	0.005%	1.0 gm.
0.25	0.05	2.9
0.25	0.10	3.5*
0.25	0.15	3.4
0.25	0.20	3.4
0.25	0.25	3.5
0.50	0.005	1.0
0.50	0.05	3.8*
0.50	0.10	3.6
0.50	0.15	3.4
0.50	0.20	3.6
0.50	0.25	3.2

*Minimum requirement for maximum growth as determined statistically by the use of the "t-test."

TABLE II

SODIUM REQUIREMENT OF THE RAT AS AFFECTED BY POTASSIUM

Potassium	*Sodium*	*Average Daily Gain for Six Weeks*
0.25%	0.005%	0.7 gm.
0.25	0.01	1.4
0.25	0.03	3.2
0.25	0.05	4.5*
0.25	0.10	4.8
0.50	0.005	0.7
0.50	0.01	1.1
0.50	0.03	3.2
0.50	0.05	4.3*
0.50	0.10	4.4

*Minimum requirement for maximum growth as determined statistically by the use of the "t-test."

Additional Na above the minimum dietary requirement may act as a partial substitute for the K requirement since the minimum shown above was thereby reduced to 0.09 per cent during the first week after weaning. The substitution effect of Na for K was gradually lost as the growth demands receded. The addition of Na to a critically low K diet had no effective substitution effect. Balance studies with rats[7] have shown subminimal Na diets do not inhibit protein digestion in the rat. A Na deficiency in the rat was shown by Grunert and coworkers[8] to accentuate and hasten the diabetogenic effect of alloxan administration. Measurements of tissue glutathione indicated that the Na deficient rat showed a marked drop in blood glutathione. Subsequent studies showed that blood glutathione decreased in Na, K, Na-K or Cl deficiencies, hence the effect was not specific per se for a Na low animal.

Elevated blood urea values were found to occur in rats fed either a low Na or K diet. This confirms earlier results obtained with other species by other workers. The accumulation of urea in the blood continues to increase over an eight week interval in the Na deficient rat, whereas the maximum concentration was reached in four weeks in the K deficient rat. The increased urea in the blood of the Na deficient rat was accompanied by a continued good food consumption in relation to body weight, table III. The ammonia nitrogen and the total nitrogen, as voided in urine, were likewise increased, table IV.

TABLE III

FEED CONSUMPTION OF SODIUM DEFICIENT AND POTASSIUM DEFICIENT GROUPS

Days on experiment	*7*	*15*	*44*
Controls	11 gm.*	10 gm.	6 gm.
Restricted feed	11	9	6
Na^+ deficient	12	11	9
K^+ deficient	12	7	—

*Grams feed consumed per 100 grams body weight.

TABLE IV

URINARY NITROGEN EXCRETION AS EFFECTED BY SODIUM AND POTASSIUM DEFICIENCIES

Days on experiment	*7*	*15*	*44*
Ammonia (mg./rat/day)			
Control	4.7	9.4	21 (180)*
Restricted feed	5.4	8.3	17 (110)
Na^+ deficient	6.0	13.0	15 (70)
K^+ deficient	6.7	14.0	—
Total nitrogen (mg. N per gram of protein consumed)			
Control	24	24	50
Restricted feed	24	30	65
Na^+ deficient	22	52	100
K^+ deficient	39	47	—

*Average weights of rats (grams).

Rats deficient in NaCl (sodium) or K consumed more water per unit of body weight than their controls.[7] Tests made to determine the effect of the dietary protein level upon water consumption showed that a significant increase in the amount of water intake occurred in those groups which received 12 per cent or 16 per cent protein in the diet. When the dietary protein was raised to 20 per cent the salt-fed group (0.5 per cent NaCl) ingested more water than those not receiving NaCl. These data are suggestive as well as challenging.

Recent work has shown that rats in a K deficient state cannot tolerate moderate amounts of "bulk"

TABLE V

SODIUM AND POTASSIUM REQUIREMENTS (GROWTH)

Species	Na+ Requirement	K+ Requirement	Ratio Na:K	Reference
Rat	0.05%	0.15–0.18%	1:4	Grunnert and Phillips
Swine	0.10%	0.20%	1:2	Meyer *et al.*
Dog	0.06%	0.13%	1:2	Elvehjem *et al.*
Man	0.59 gm./day	1.28 gm./day	1:2	Reimer *et al*
Chicken	0.12%	0.33%	1:3	Burns *et al.*
Cattle:				
Dairy	.15%			Smith *et al.*
Beef	.13%			Smith *et al.*

*Calculated from data for "young adult male."

feeds. The inclusion of 19 per cent cellulose in the diet caused frequent deaths in the rat low in K while those fed adequate K remained healthy and vigorous. Death of the K impoverished rats was due to intestinal compaction.[9] Studies to determine the cause of the compaction revealed that there was a great loss of the propulsive motility of the intestine in the K deficient rat.[10] Further work has shown that B-methyl-acetylcholine stimulates the peristaltic activity of the intestines of rats receiving potassium-deficient diets.[20]

Swine. The requirements of swine for Na and for K are similar to those of the rat. The type of ration influences the need for either element. Growing and fattening swine fed a ration composed of natural feeds were thrifty when fed a balanced ration of commercial ingredients that contained 0.06 per cent Na.[11] Meyer and coworkers fed this type of ration with only 0.02 per cent Na and succeeded in fattening market pigs. By means of a purified diet Meyer and coworkers[12] found that the requirements of young growing pigs were met by 0.09 per cent Na. Balance studies indicated that this level was the one at which maximum Na retention occurred. Pigs fed suboptimal Na retained only 87 per cent of the Na ingested. These data would indicate that there was a constant daily loss of Na and that appropriate allowances should be made for this fact in formulating rations for optimal growth. In passing it is interesting to note that the limiting factor supplied by salt appeared to be the Na ion.

For optimum growth the K requirement for pigs was found to be about 5 grams of K per 100 pounds of body weight, or about 0.20 to 0.25 per cent of the ration. The authors point out that the rate of gain in body weight determines the amount of K needed in the ration. Studies, by Meyer,[11] with sows in lactation indicated that 0.03 per cent Na met the requirements of this species. The colostrum milk from the sows contained 0.08 per cent Na while milk contained only 0.04 per cent.

Salt sickness in growing pigs was produced by Grummer and Bohstedt.[14] This was accomplished by conditioning pigs to the ready consumption of a liquid ration which was readily and quickly gulped or eaten, and by the addition of 2 per cent salt. The pigs became "salt sick" and died of a paralysis, not unlike that shown by the K deficient dog.

The dog. Very little work has been done on the requirements for Na and K in the dog. They behave nutritionally like the rat and pig, and this fact would indicate that the requirements would be similar. A K deficiency in the dog causes paralysis.[13]

Michaud and Elvehjem[15] estimated the requirements of the dog to be 0.06 per cent Na and 0.13 per cent K.

Man. The Na and the K requirements of man have not been critically studied. Reimer and coworkers[16] presented data from balance studies with humans which indicates a requirement of 0.58 grams of Na per day and 1.25 grams of K per day. These data would indicate, percentagewise, roughly 0.06 per cent Na and 0.21 per cent K were needed in the ration of man.

Chicken. In this species the rate of growth determines the requirement for the growing chick. The need for Na during the rapid growth period has been shown by Burns and Cravens[17] to be 0.12 per cent while the mature bird survives without apparent difficulty when fed on only 0.05 to 0.06 per cent Na. The K requirements for fast gains in weight have been shown to be 0.3 to 0.4 per cent K. These figures are rather surprising in view of the fact that poultry can withstand extraordinary amounts of salt in their rations.

Ruminants. Ruminants such as cattle, either beef or dairy, develop a marked unthriftiness in the absence of NaCl. The requirements for this species can be met by 17 to 31 grams of Na per day. Minimal amounts are difficult to determine. This is estimated to be 0.12 to 0.15 per cent.[19,18]

SUMMARY

The dietary requirements for Na and K were found to be 0.05 per cent and 0.15 per cent respectively as measured by growth in the rat. These requirements apply to several species including the rat, dog, pig, and probably cattle and poultry. The Na:K ratio is critically important if high levels of Na are fed with low levels of K, otherwise the total intake of either Na, K or both is the more critical. The requirements for Na and K are modified upward 50 to 100 per cent during the rapid growth period. They are also modified by the customary diet of the species.

Subminimal dietary Na and K results in an increased water consumption and elevated blood urea without impairment of kidney function (as measured by nitrogen excreted per gram of protein consumed). A Na deficiency in the rat increases its susceptibility to alloxan administration. A K deficient rat develops intestinal stasis which can be relieved by the administration of B-methyl-acetylcholine.

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DISCUSSION

DR. FOLLIS: Dr. Cannon's presentation has been of particular interest to me as it undoubtedly has been to the entire audience. I am sure the interrelations with other elements which one has to consider in studying the deficiency of a single element are important. Whether the lesions that Dr. Cannon showed us are due to Na intoxication or K deficiency, I think, is yet to be settled. There is the possibility, of course, that the excess Na is forcing more K out. I was extremely interested to see the areas of necrosis in such large measure without any inflammatory reaction about them. I am sure you were shocked when you saw them, as I am this afternoon, because it is difficult to realize.

The lesions in the liver are also extremely interesting. We have never seen anything like this in our own material. They are identical with lesions one can produce by a deficiency in methionine. Dr. Phillips mentioned the influence of a diet of high fat content.

DR. DARROW: The finding that impressed us when we first saw the cardiac lesions of K deficiency was the extraordinary difference in animals subjected to similar diets and injections of desoxycorticosterone. I know we didn't do the experiments with the best techniques since several animals were kept in a cage and would not be expected to consume the same amounts of food. I was impressed by the fact that you couldn't see the lesions in one rat in the group, although others showed extensive lesions.

We ran across the fact that Na was necessary for the production of cardiac lesions, although we didn't pay particular attention to this observation, because we were interested primarily in other aspects of the problem. You do not get marked changes in muscle composition of rats fed diets low in K unless considerable NaCl is also given.

We had difficulty keeping the rats alive after the third or fourth week. Our diets were not as deficient in K as was the case in most of the similar studies. There was an excess of Na over Cl. We noticed that the rats were dying off after the third week, although some went as long as 56 days.

I shall add a comment not made at the meeting. Cooke and Segar have experiments on rats which involve giving a diet low in K, Na and Cl and offering variable amounts of bicarbonate as $NaHCO_3$ and $KHCO_3$ and small amounts of Cl in the drinking water. The load of bicarbonate that must be excreted is high. If no K is present in the drinking water, alkalosis develops, but if K is present, no alkalosis develops. At present they are attempting to see how little K is necessary to prevent alkalosis with the load of bicarbonate. It looks as if a very small amount suffices. It is too early to draw conclusions. It appears that K does not function in the excretion of bicarbonate through its substitution for Na in tubular urine but rather by preventing some deficit in cells developing that interferes with ion transport. We are inclined to believe that alkalosis is not readily produced without concomitant K deficiency. I would like to make the following comment on this point. It seems unlikely that the level of K in the cells is as important as the difference in hydrogen ion concentration on the two sides of the membrane. Even in K deficiency there is considerable K in the cells and the difference in K concentration is going to be considerable between the two sides of the membrane. I suspect that this difference in K concentration on the two sides of the membrane is altered by the hydrogen ion concentrations. I don't believe this phenomenon will correlate with cellular K concentration but rather with the differences in concentration of certain ions of which hydrogen is likely to prove crucial.

DR. BOYER: I was wondering further on this subject if actual tissue analysis had been done on these animals to show how much Na entered the tissue at the time the lesion appeared, and how extensive was the depletion of K. I would like to get a quantitative relationship.

Another point in relation to K-Ca antagonism. I wondered if there was any relationship between the Ca level in the diet and the toxic effects that you get due to K lack.

DR. RANDALL: I would like to ask Dr. Cannon whether he has observed any changes in the kidneys of these animals which died with K depletion and Na retention.

DR. GARDNER: We have seen the excretion of a large urine volume in rats depleted of K by dietary means. A 200-gram rat might excrete as much as 75 ml. of urine per day, having been chronically depleted of K. We are interested in this phenomenon, and we have no very good idea as to what causes it, whether it be due to a renal lesion per se or to a lesion in the region of the hypothalamus.

CHAIRMAN RUBIN: I wonder about lesions occurring in the inner lining of the heart and about subendocardial fibrosis. Also, whether the rat would drink Na water instead of K or the reverse and whether they would make a self-selection diet.

DR. CANNON: In answer to Dr. Follis I would say that, although at this time one cannot be sure that these lesions in K-deficient animals are due entirely to the toxic action of Na, I believe the evidence is very good that they are. Of course, as Dr. Darrow and his associates have shown, as K ions pass out of cells, both Na ions and H ions come in. Therefore, part of the toxicity may also be due to an effect of H ions as well as Na ions. I do not believe the effects can be attributed to amino acid or vitamin deficiencies, because these lesions appear after NaCl injections in animals which are taking their full daily complement of amino acids, vitamins and salts, except K. The amino acid solutions have a high content both of cystine and methionine.

With respect to the development of renal lesions, the kidneys are enlarged, with dilated distal tubules and with evidence of epithelial hyperplasia. An interesting fact is that this occurs also in animals getting both a

low K and a low Na intake. I do not know how to explain this. Perhaps Dr. Peters may wish to comment on this in relation to the problem of renal function.

I was interested in Dr. Darrow's comments because he and others have described these myocardial lesions in growing rats injected with DOCA. So far as I know, only the workers of the Wisconsin group (Meyer and coworkers) have reported an increased severity of these lesions in relation to high intakes of NaCl. Although there are a few case reports of so-called K-deficiency myocardial necroses in human subjects, the lesions are considerably different from those observed in lower animals. It may be that with better methods of fixation and staining, the lesions in human being may be more adequately studied.

In answer to Dr. Boyer, my reply is that it was largely on the basis of his work and that of his associates that I raised the question, whether it might not explain these intracellular changes in the myocardial fibers. Several workers have shown an increased Na content of such hearts, but I presume it will require histochemical technics not yet available in order to clarify the question of Na and K contents within individual cells. All I can say now is that the lesions are those characteristic of chemical action without cellular accumulations. My best guess is that they must be associated with an intracellular ionic disequilibrium, and your work and that of others points strongly to the possibility that this may be a consequence of intracellular enzyme disturbances.

We have not made any studies as yet concerning the K-Ca relationships.

I cannot answer the question as to the relation of these lesions to subendocardial fibrosis in infant's hearts. Neither do I know why these K-deficiency lesions tend to localize subendocardially, nor why there is so much variability in animals and in distribution within the heart. There must be a great range of differences in degrees of K depletion. Our animals are both protein-depleted and K-depleted, and, because of the repletion processes, it is probable that the necrotizing lesions develop more extensively than they do in growing animals not subjected to such metabolic stimuli.

We do not seem to have much of a problem with respect to self-selection. Our animals accept both the basal ration and the amino acid solution almost completely until relatively late in the state of K-deficiency. Then, their appetites decline somewhat, but never to the extent seen under conditions in which an essential amino acid is removed from the ration.

DR. PHILLIPS: I have a few comments that might be enlightening, although they do not answer the questions.

We have noted an increased urine volume, when rats became K deficient. This occurs along with the elevated urea in the blood. Temporarily we have had to go along on the theory that the additional water intake was due primarily as a means of eliminating urea.

We have not tested the Ca-Na relationships. We have produced lesions in the heart due to a change of ionic balance. We found one factor that produced a necrosis of the heart muscle, namely, a disturbance in the Mg-Ca ratios. It occurs most frequently on a low Mg diet. Just what this means, I don't know. We cannot always protect them against the development of lesions with ample magnesium; so there is something there in the relationship of Na, K, Ca, Mg, that still needs clarification. A little more work is indicated.

We have not considered our wide ratios (a minimum amount of K with an excess of Na) as being a toxicity phenomenon. It may well be. That is a new thought as far as I am concerned. We consider it more of an imbalance between the cations, and there is some evidence to support this point of view.

In relation to the pathology, Dr. Constant, in our laboratory, has done considerable work on the pathology of the whole K-low-Na rats, and in general we have confirmed the results of Dr. Cannon; but, like Dr. Follis, we have not been able to demonstrate anything in the liver, other than a collection of lymphocytes; but maybe it is an earlier stage, and, perhaps, we have not been critical enough. In general, our results agree with Dr. Follis' in their basic pathology and I believe we have had traces of what Dr. Follis' work suggests. It is difficult to get a Na-deficient pig if he has access to urine. They consume large quantities of excreta in order to re-establish the Na-K intake levels. This holds to some extent with rats, although we have not made definite self-selection experiments to test this last point.

CHAIRMAN RUBIN: Because of the relationship of the next three papers we will reserve the discussion until Dr. Keith has finished.

Physiology of Renal Excretion of Potassium

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THE FACT that K is both reabsorbed from and secreted into tubular urine[1,2] makes analysis of its excretion peculiarly baffling. Since it appears possible to retard the two processes separately, they are probably not reciprocal, but coexisting activities.

Although the excretion of K diminishes when the supply of the ion is limited, it does not so nearly cease as does that of Na. Adult animals will, therefore, develop deficiencies of K, but not of Na, when the dietary intake of the two elements respectively is reduced.

The control of the quantity of Na and Cl in the body must be exercised through the kidneys since these ions reside predominantly in the extracellular fluid. Potassium on the other hand is naturally a constituent of cells. Nevertheless, its concentration in extracellular fluid has crucial significance because deficiencies or excesses of K generally manifest themselves overtly only if they are reflected in comparable disturbances of concentrations of K in the extracellular fluid. Although K must be a major contributor to the osmotic pressure of cellular contents, its concentrations in the cells can vary considerably with the cellular load. The cells tend to maintain their own supplies of K and at the same time to protect its concentration in the plasma. In the face of a deficiency the plasma is protected at the expense of the cells; part of any surplus load is ab-

sorbed by the cells to be delivered as the extra K is excreted. The fact that the cells provide this protection makes serum K less reliable than serum Na as an index of the quantity of ion available for excretion. In the case of a deficiency, the K given off by the cells is replaced by Na and H ions through ion exchanges. The cells respond to some changes of acid-base equilibrium in a similar manner. They also alter their loads of K and phosphate in response to alterations of carbohydrate metabolism or their loads of protein. Potassium, however, is relatively unconcerned about osmotic pressure per se.

Secretion and active reabsorption are effected by movements of salts in their entirety and by ion exchanges. The transfer of K and phosphate with carbohydrate requires no ion exchange. This is true also of the movement of the segment of NaCl concerned with the maintenance of osmotic equilibrium and the distribution of fluids in the body. Of the enormous amount of NaCl reabsorbed, it has been suggested that a major fraction is returned from the tubules by a simple process of back diffusion, the residual fraction by an active process partly under hormonal control. In addition, a certain amount of Na must be returned by ion exchanges with K, H and ammonia. The delivery of some Na to the urine, that is secretion of Na, cannot be unequivocally denied because the amounts reabsorbed are so stupendous that secretion would be undetectable; but secretion of either Na or chloride seems superfluous.

The magnitude of the irreducible leakage of K is compatible with passive back diffusion like that suggested for Na in the proximal tubules. Some might also be actively withdrawn from the tubules in association with phosphate and other anions. Active reabsorption by ion exchange with Na seems unlikely because it would entail secretion of Na. This is the predominant activity of Mudge's[3] slices of renal cortical substance. This raises the question whether the behavior of these slices is relevant to the reaction of the tubular cells to the contents of the tubules.

It has been suggested by Pitts[4] on the basis of experiments with the inhibition of carbonic anhydrase that K participates with Na in the ion exchanges with H by which the urine becomes acidified. By use of a stronger inhibitor of carbonic anhydrase, 6063, Berliner, Kennedy and Orloff[5] found that the urinary increment of K evoked by inhibition of carbonic anhydrase is a product of secretion. They have suggested that K and H are in competition for the same mechanism in exchange for Na. This explanation is unsatisfactory because the changes in K excretion are not accompanied by comparable changes in the excretion of bicarbonate. Furthermore, if there were such competition between K and H, it should manifest itself in alkalinization of the urine when K secretion is increased.

It is hard to conceive any mechanism other than ion exchange by which secretion of K could be accomplished. Molecular secretion of K salts would entail the secretion of anions for which there is no evidence or need. If K is withdrawn from the diet, its concentration in the serum gradually falls, the quantity in the cells also diminishing; excretion reaches minimal proportions. Desoxycorticosterone acetate accelerates the cellular discharge of K and its excretion. In both cases the K in the cells is partly replaced by Na. If Na is withdrawn from the diet, DCA increases neither the excretion nor the cellular loss of K.[6] Attrition of K may represent mere failure of reabsorption in which K takes the initiative. The action of DCA indicates secretion of K, but Na seems to play a primary role in activating the secretory ion exchange.

If a large amount of K is given over a long period, a considerable quantity is taken up by the tissue cells and its excretion increases strikingly. A similar outflow of K is provoked by measures that increase the concentration of Na in the serum. This secretion of K is not a response to dehydration of the cells or increase of the intracellular concentration of K as Mudge, Foulks and Gilman[2] have suggested because it is not induced by injections of mannitol and other substances that increase the effective osmotic pressure of the extracellular fluids without increasing the concentration of Na.[7,8] When the amount of K in the cells rises out of proportion to other cellular constituents, the kidneys secrete K. When there is a demand for maximum reabsorption of Na, the same ion exchange mechanism is brought into play for this purpose. This leads secondarily to the discharge of K into the urine. The mannitol experiments indicate that the cells are indifferent to changes in the intracellular concentration of K provided the concentration of other cellular constituents is proportionally altered. There is little evidence that Na enters cells when these are contracted by osmotic disturbances. The augmentation of the excretion of K by the administration of Na may be referable to displacement of Na from the cells by K.

In K deficiency, K which escapes from the cells is replaced by Na and H ions, the serum becoming alkaline.[9] Administration of K salts reverses these reactions. Induction of a rise of pH by overbreathing, administration of bicarbonate or loss of Cl causes ion exchanges similar to those of K deficiency. Acidification causes transfers in the opposite direction.[10] In these exchanges, like those in the kidney, either K or Na may take the initiative.

Mercurial diuretics facilitate the excretion of NaCl by checking its reabsorption. When given with a water load which does not by itself affect the excretion of K, a mercurial diuretic accelerates the excretion of both Na and K. This has been attributed by Mudge and coworkers[1] to inhibition of reabsorption of K. If a mercurial is given during an infusion of a K salt great enough by itself to activate the secretion of K, the excretion of K is decreased while the excretion of Na is facilitated. This suppression of K excretion which Mudge and coworkers ascribe to

inhibition of K excretion could equally well be attributed to inhibition of the reabsorption of Na by the same ion exchange process.

It has been suggested that the reabsorption of K may consist partly of passive back diffusion, partly of active molecular transfers; ion exchanges are improbable because they would involve the secretion of Na or anions or the participation of K in the renal adjustment of acid-base equilibrium. That group of reactions in which alterations of the excretion of K and Na parallel one another could arise from variations of reabsorption. Secretion of K is most simply explained by an ion exchange with Na, in which reabsorption of Na is implicit. There is no reason why this process should not be activated in behalf of Na as well as K. It would account for that group of responses in which alterations in the excretion of K and Na are reciprocally related. Explanations for variations of excretion of K must be sought at tissue cell boundaries, if only because the K available for excretion is determined at that point.

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The Role of the Kidney in Potassium Depletion

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The problem under consideration involves somewhat arbitrary separation and isolation of two facets of an intricate, interacting group of metabolic processes. For example, both depletion of K and renal function appear to be inextricably linked to the metabolism and excretion of other electrolytes, of water, carbohydrate, and of protein; in addition they are influenced by, and probably reciprocally alter, underlying disease processes and endocrine relationships. This viewpoint is proferred as an alternative to the implication that both K metabolism and renal function tend to have self-generating, self-sustained patterns of behavior.

In contrast to the deluge of investigations of K deficiency in clinical situations, there are few data concerning this problem in normal human subjects sustained on diets optimal in all other respects. The results of a recent study[1] by Black and Milne of two normal human subjects maintained on a strikingly reduced K intake of nine milliequivalents per day are perhaps most pertinent; nevertheless the diet was unusually rich in Na, Ca, and phosphate so that K was not the only variable. Depletion of K to the extent of approximately 5 per cent of body stores, and abnormal depression of the concentration of serum K, occurred within 7 days. This depletion was mediated primarily by persistent loss of K in the urine so that even on the last day of low intake about 20 milliequivalents were excreted. On the basis of what Dr. Gamble has described as the Bunge phenomenon,[2] it might be anticipated that a lower intake of Na would have resulted in greater renal conservation of K. Nevertheless, these and other findings[3,4] are consistent with the view that in general urinary excretion of a significant quantity of K may continue despite limited intake of the ion and a falling concentration of serum K. These facts appear to contrast sharply with the results of ingestion of a diet low in Na: Under these circumstances renal conservation of Na is usually more precise and complete—as shown by McCance[5] and others.

What then of the role of the kidney in producing deficits of K in ill patients whose intake of the mineral has been restricted, but in whom kidney disease is not present. Whether or not losses of K accrue as a consequence of diarrhea, steatorrhea, vomiting, intubation and suction, fistulae or other extra-renal sources, continued renal excretion of the ion usually accounts for a highly significant fraction of the net depletion. This does not necessarily imply that a fall in concentration of *serum* K (in contrast to over-all depletion of bodily stores) is determined solely by external losses in the urine or via other channels. As a matter of fact even when the urinary excretion of K is very rapid, its serum concentration may be abnormally elevated or normal notwithstanding profound net depletion of the substance. The reduction in plasma K frequently takes place subsequently when urinary and other losses are diminishing. Such a reduction in serum K appears to be attributable to such interlocking factors as rehydration, resumption of utilization and storage of carbohydrate and protein, and transfer of K into the intracellular phase. This sequence of relations between extracellular K and its renal excretion is perhaps most vividly (and easily) documented in diabetic acidosis,[6] but appears to be equally valid in other varieties of profound dehydration and electrolyte depletion. In addition an analogous reduction in the urinary excretion of K has been observed in association with diminution of serum K during induction

of paralytic episodes in patients with familial periodic paralysis.

Stores of body potassium tend to be depleted in patients given pituitary adrenocorticotrophic hormone, cortisone, desoxycorticosterone, and licorice extract (glycyrrhizin) because of augmented urinary K excretion. These findings have led to the hypothesis that the increased excretion of K during uncontrolled diabetic acidosis, in the postoperative catabolic phase, and in many other types of dehydration and electrolyte depletion is provoked by overactivity of the adrenal cortex. Certainly the fact that injected animal products and synthetic materials with adrenocortical-like activity increase K excretion is consistent with the aforementioned theory. Nevertheless these observations are equally consistent with, and do not cogently exclude, alternative hypotheses.

The latitude of urinary excretion of K in patients with K depletion requires further emphasis. Thus during phases of rehydration, repletion of electrolyte, reversal of the reaction to injury, and less frequently in other circumstances, renal conservation of K may be so precise and complete that the concentration of K in urine is below that of plasma[7,3] and the excretion rate of K is negligible.

There remains the interesting problem of urinary excretion of K and detailed renal mechanisms producing deficit of the ion in patients with renal insufficiency. The fact that patients with renal insufficiency run the gamut of possibilities—intoxication, normal stores of K, or depletion—describes a versatile urinary excretory pattern in the face of renal disease, although such versatility may not be apparent in a given patient during a discrete period of study. Urinary loss of K may be sufficiently profound, although transient, as to constitute an important factor in producing deficiency in a manner comparable to that noted in normal subjects and in patients with K deficiency without renal disease. That this urinary loss of K may contribute to the development of deficit notwithstanding the presence of advanced renal insufficiency seems paradoxical in view of the usually limited excretory powers of such patients in disposing of exogenous loads of K, but it is nonetheless factual. That is to say, in many patients with renal failure, urinary excretion of K is in a sense sufficiently normal to contribute to deficiency of the ion when intake is curtailed and/or extra-renal losses of K supervene.

Perhaps more startling is the rare occurrence of prolonged wastage of K in the urine of patients with either the usual stigmata of renal insufficiency or peculiar variants presumed to be dependent upon isolated disturbances of reabsorptive, secretory, or ion-exchange processes within the kidney.[8] Excessive excretion of K under these circumstances occurs despite adequate intake of the ion, and in some of the patients when the metabolic state does not appear to be conducive to accelerated excretion of K as judged by the onset of K depletion in other subjects with or without renal disease previously discussed. This state of continuously negative balance of K may in certain instances be correlated with profound generalized derangements which include intermittent paralysis. The accompanying table lists some of the syndromes, rather ill-defined and overlapping, in which chronic urinary wastage of K has either been established or inferred.

Finally some believe that in certain patients with renal insufficiency K may be either secreted by the renal tubule or that the increment of K found in the urine is a significantly larger fraction of the K filtered by the glomeruli than is normally the case. This hypothesis rests upon the supposition that the clearance of insulin, creatinine, and their relatives is in fact a measure of the net rate of glomerular filtration. One of the staunchest proponents of the validity of insulin clearance in this regard, Professor Smith, has pointed out[9] that insulin clearance may be an inaccurate measure of glomerular filtration rate in patients with renal disease. Furthermore, A. V. Wolf and others have adduced evidence against this assumption even in the normal organism.[10] Therefore, although the possibility of secretion of K by the renal tubule is undeniable, current methods of study of renal clearance apparently fail to establish it.

It may be appropos of the studied deliberations of this symposium to conclude with the following limerick:

There once was an ion named K
That cured many ills of our day
Atomic weight thirty-nine
Flame photometers define
Dilemmas which many dismay.

TABLE I

RENAL DISORDERS THOUGHT TO BE ASSOCIATED WITH PERSISTENT WASTAGE OF POTASSIUM IN THE URINE

1. Advanced chronic renal insufficiency
2. Allegedly specific renal tubular disturbances
   a. "Renal acidosis with osteomalacia"
   b. "Hyper-ammoaciduria; Fanconi syndrome."
3. Overlapping categories 1 and/or 2-a and/or 2-b.

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The Significance of Potassium in Uremia

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The conception that there might be a disturbance of K metabolism in uremia was discussed and investigated experimentally in 1881 by Feltz and Ritter.[1] These investigators actually demonstrated, by chemical analysis of a large sample of blood, an abnormally high concentration of K in experimental animals, in which the ureters had been ligated. The introduction, in 1921, by Kramer and Tisdall[2] of a quantitative microchemical method for estimating K gave a fresh impetus to the study of the distribution of that ion throughout the tissues of the body. But it was not until 1938, 1940, and 1941 that Winkler, Hoff, Smith,[3,5] Winternitz and associates[4] established two important facts with regard to K and uremia. Their first contribtion was the observation that a rapid injection of a K salt into a vein of an experimental animal leads quickly to an abnormal increase in the concentration of K in blood serum and that, when it reached a concentration of 13 to 15 mEq. per liter, cardiac standstill occurred. Their second discovery was that a similar sequence of events took place after bilateral nephrectomy or bilateral ligation of the ureters or renal arteries. In these experiments, repeated electrocardiographic tracings revealed premonitory and terminal alterations, which appeared to be specific for K intoxication.

The next immediate problem was to ascertain whether these experimental facts were pertinent to human renal insufficiency. In 1939, we observed[6,7] in a patient suffering from terminal uremia, a similar correlation between the development of hyperpotassemia and certain electrocardiographic patterns. Finch and Marchand reported a similar experience in 1943,[8] but in addition obtained a continuous electrocardiographic record up to the time of death. Ventricular fibrillation preceded the final standstill. Pathologic studies of such hearts have so far failed to reveal any distinctive lesions.

How often then does K intoxication play such a serious role in uremia? Fortunately it occurs infrequently. In our renal clinic, over a period of seven years of watchful expectancy, we observed only 13 cases of serious hyperpotassemia.[9*] The concentration of K in blood serum in these cases varied between 7.7 and 10.5 mEq. per liter and simultaneous electrocardiograms revealed alterations indicative of hyperpotassemia. Thus, the occurrence of toxic effects on the heart was not directly related to the actual concentration of the increased serum K. This fact was pointed out by Darrow and associates in the cat in 1943.[10] The concentrations of serum K in human uremia are lower than those reported in experimental uremia in the dog and cat. Among the several possible reasons for this species difference are the frequent concomitant changes in the concentration of other electrolytes in human blood serum. Our studies, however, have not as yet indicated a definitive ionic pattern. In human hyperpotassemia, there appear to be several possible and variable etiologic factors involved, which include the patient's state of nutrition, the presence of anorexia and vomitings, diarrhea, dehydration, and the degree of renal insufficiency. We, along with others, have observed concentrations of serum K in normal persons and in uremic patients within the toxic uremic range, 7.7 to 9.6 mEq., without evidence of intraventricular block in the electrocardiogram. The rise in serum K was usually of short duration and in several instances was noted while the content of the individual's diet was low in Na and water.

The diagnosis of toxic hyperpotassemia is often difficult. These patients do not develop a typical clinical syndrome. Rarely nervous manifestations occur and give one the clue to the underlying disturbance. These include marked asthenia, localized paresthesias, and sometimes paralysis of both upper and lower limbs. The occurrence of quadriplegia in cases of uremia have been reported by Finch and coworkers[11] and McNaughton and Burchell.[12] In the latter's patient, within five hours of the intravenous administration of 1000 cc. of a solution containing 9 gm. NaCl., 1.0 gm. calcium gluconate, and 5 gm. of dextrose, there was complete recovery from the paralysis and the electrocardiogram was nearly normal. In 18 hours the serum K had fallen from 8.6 to 5.3 mEq. and the electrographic tracings were normal. Thus, K intoxication appears to occur rarely in uremia, but its development is of serious import and in a patient with reversible renal function, its recognition and the institution of proper therapeutic measures may be life saving.

Paradoxical as it may seem, hypopotassemia can occur in uremia. We observed its occurrence in a patient in 1936.[13] In a second patient seen in 1946,[14] cessation of anorexia and the ingestion of an adequate diet for several days replenished the depleted K stores. Brown, Currens, and Marchand in 1944[15] reported the development of muscular paralysis in

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*It is quite possible that cases of hyperpotassemia occur more often in uremia. Our series of cases did not include strictly urologic conditions. More frequent estimations of serum K and electrocardiograms in uremia closer to the terminal event might also reveal more instances of toxemia.

a uremic patient, in which the electrocardiogram indicated hypopotassemia. Sherry and associates[16] noted, in a case of chronic nephritis with a complaint of transient attacks of muscular weakness, hypopotassemia (1.5 to 2.5 mEq. per liter) and the associated electrocardiographic changes. With due consideration to the low nutritional state sometimes present in chronic uremic patients, one can readily understand why the K content of such a patient is depleted.

The knowledge that there can be abnormal shifts in the concentration of K in blood serum, either an increase or decrease, during the course of uremia, suggests the possibility of the development of both hyperpotassemia and hypopotassemia in the same patient. Last year, Bernreiter and Calovich[17] reported a case of uremia, in which typical electrocardiographic tracings indicative of both conditions were observed, although estimations of serum K were not made. During the patient's initial coma, the electrocardiogram revealed a complete auriculoventricular block and a prolonged Q-T interval. The patient was given intensive therapy by vein, 25,000 cc. of fluid by that route in seven days. During this period, the patient developed severe diarrhea, vomiting, excessive sweating, and paralysis of both arms and legs. The electrocardiogram showed the typical depression of the S-T segments seen with hypopotassemia. With the administration of KCl the paralysis disappeared and the electrocardiogram returned to normal.

Because of the difficulties of recognition of disturbances of K metabolism, we were led to investigate the K tolerance[14] in a series of ten cases of uremia. It was the rule for these patients to have a diminished tolerance, but it was interesting that in only a single case did there develop a transitory intraventricular block in the electrocardiogram; on the other hand, in another case the curve of the serum K indicated a reduction in the stores of K.

Disturbances of K metabolism have been proven to occur in the uremic state. They can cause serious dysfunction of muscles and nerves, and cardiac standstill. Detection of the disturbances is important and is made usually by estimation of serum K and the electrocardiographic tracing. Induction of appropriate therapy may reverse the processes.

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DISCUSSION

DR. RUBIN: Dr. Peters brought out the points about the kidney in relation to the K concentration of the glomerular and tubular filtrates. Dr. Tarail brought out the point that in renal disease the K composition is concerned with a disturbance of tubular function, either excretion or reabsorption, and I think, in addition to that, the composition of the body also alters the composition of the K in the urine. It is pretty obvious that there are a large number of opinions as to the mechanism by which renal function controls K metabolism.

Since Dr. Peters started off with a discussion of Dr. Berliner's theory, we will ask if Dr. Berliner might start the discussion.

DR. BERLINER: I would like to comment on Dr. Peters' comment on our data and our hypothesis. I might briefly state the hypothesis in order to bring the interpretation of the data into line. The hypothesis that we have suggested is as follows: that in the secretion of K and the secretion of H ions, both of which are presumed to be in exchange for Na, these ions are in competition at some point in the secretory processes. Consequently, changes in one will be, in general, reflected by reciprocal changes in the other. However (and this is important), these are not in equal proportions.

As to the experiments on which Dr. Peters commented: the first experiment was one in which the animal was phosphate loaded, and it so happened that in this particular experiment the change in K and change in phosphate were parallel. However, that has not been our experience in many of a large number of experiments, in many of which there has been practically no phosphate in the urine at all. The changes in K excretion are of equivalent magnitude whether or not phosphate is present.

In the second experiment, Dr. Peters commented on the fact that bicarbonate excretion did not change when the effect of the mercurial was abolished. One must remember that the effect of 6063 does continue, however. We visualize the situation under conditions where both the mercurial and 6063 are acting as a marked depression of both hydrogen ion and K secretion. Now, when the K secretion is liberated from inhibition by the mercurial the only thing that can happen (there being no possibility of a change in H secretion) is that there be a rise in K excretion balanced by an equivalent decrease in Na excretion. Of course, this cannot be demonstrated in the data, because there is, at the same time, a drop in the rate of Na excretion, from nearly two mEq. per minute down to a few hundred microequivalents per minute as a result of removal of the mercurial effect. Of course, we can't say specifically "this much" of that drop of Na excretion is due to the (relatively small) increase in K excretion.

Dr. Peters has questioned the validity of the hypothesis since, in the certain clinical abnormality which he indicated, the administration of K did not produce an

alkaline urine. I would say, however, the great preponderence of data does indicate that, when K salts are administered, the urine does tend to become alkaline. Furthermore, K excretion is increased when alkali is administered and inhibitors of acidification other than those affecting carbonic anhydrase produce similar effects on the secretion of K.

DR. BUTLER: I would like to emphasize the importance of the electrocardiogram in appraising the state of K metabolism of a patient. It is generally recognized that there is the possibility of there being hyperpotassemia in the uremic patient. We have been impressed recently with the occurrence of K depletion in patients in whom renal insufficiency and vomiting has resulted in a markedly elevated N.P.N. On admission, though the serum K may be either normal or slightly elevated, an electrocardiogram may indicate K depletion. We have administered intravenously solutions containing 25 to 75 mEq. of K per liter to such a patient with striking clinical benefit. In the presence of an electrocardiogram indicative of K deficiency in a uremic patient one should not be afraid of giving K as a part of the therapy. Dr. Richard Neubauer has also demonstrated marked K deficiency in uremic patients with marked improvement with retention of administered K.

Dr. Peters' warning about the difficulty of interpreting the electrocardiograms can, I think, be minimized by following the changes occurring at short intervals during infusion therapy. You depend upon serial electrocardiograms where you follow changes incident to therapy and clinical state of the patient.

DR. GUEST: I should like to ask Dr. Keith if different patterns of "K tolerance" curves could be related to changes in pH of the blood. In studies I shall present tomorrow we found evidence that lowering of pH may inhibit cellular uptake of K and phosphorus from the blood.

DR. OLLIS: I should like to ask another question of Dr. Butler. What happened to your electrocardiogram and your serum K and how did you determine the amounts of that?

DR. BUTLER: In our opinion you can estimate the amount of K by following the electricardiogram. The blood level of one of the patients fell after the initiation of hydrating therapy. In one patient we overdid the K therapy as reflected by a change in the electrocardiogram. It could be demonstrated that the electrocardiogram could be modified by K therapy. After we diminished the K, it again showed a need of increase.

DR. VISSCHER: I hesitate to do what I am going to do right now because it may sound like "confusion thrice confounded," but I feel as if I should raise a question of a basic nature. We are trying to assume, on the basis of evidence that certainly is very indirect, that what happens in renal secretion is a process of ultra filtration, and beyond that point, with respect to water and ions, there is pretty much a one-way movement from the tubular fluid into the blood. There may be, as has been mentioned here, some evidence of secretion into the tubules of K, but there is no suggestion that there is exchange. I want to call your attention to the fact that the best evidence that we have for filtration absorption and selective reabsorption with regard to ions, comes from the Richards data, and others following him, on the frog kidney. Our information on the intact mammalian kidney is awfully roundabout.

I make this elaborate introduction to a report of some work by Messrs. Tom Hoshiko and Robert Swanson in the laboratories of the Department of Physiology here, because it will immediately be objected that their observations are on a dying kidney. I am going to simply point out that all the observations that I know about that are crucial, and on which we base our theories, are also on dying kidneys. They have found by perfusing the renal portal and renal arterial systems and, using suitable tracers, that there is exchange—or let us say, there is equilibration of the urine with water in the renal venous system, which is approximately 100 per cent equilibration With respect to Na and K, it is 50 per cent, or thereabouts. In other words, in this frog kidney, there is evidence that there is a very large movement of cations from the tubular spaces into the tubular fluid. I wouldn't suggest it is necessarily a normal phenomenon. I only call attention to the fact that our theories with regard to what does happen are based upon observations on the same kind of dying preparation. It may therefore be that two-way movements of water and certain ions across the renal tubule are normal processes. If so, the kidney tubule must possess mechanisms for determining the rates of movement of, for example, Na in the two directions. The relative magnitudes of those rates will then fix the final excretion rate.

DR. CARPENTER: Have you any evidence or do you know of any that balance can be achieved in a normal individual or normal animal on K restriction? We have given 8 to 10 mEq. of K in a diet to a normal individual for about 12 days, but as the secretion was increasing we wondered whether a balance had been obtained. I also would like to emphasize the acute K deficiency cases that do occur. I agree with Dr. Tarail that acute cases do result from decreased intake but that chronic cases are very rare.

DR. MUDGE: I would like to emphasize one point which Dr. Peters has made in reference to the slice studies. I think we would all make a tremendous mistake to extrapolate from the slices to the intact kidney. We don't know enough about the basic mechanisms of ion transport to be able to compare directly experimental data derived from such different types of studies.

DR. PETERS (in answer to Dr. Carpenter): In partial answer to Dr. Carpenter's question about K balance on a low intake, I believe we have data on at least one reasonably normal individual in whom, during a metabolic study, a positive K balance was attained and maintained with a K intake of less than 10 mEq. per day. I trust that Dr. Butler may have something to say about this.

DR. PETERS: In answer to Dr. Berliner's defense of his claim that K and H compete with one another in the ion exchange with Na, I am glad Dr. Berliner has shown me the errors of my ways. Nevertheless, I still do not feel that his explanation is inevitable. I cited Dr. Earle's case particularly as one that exhibited secretion or wasting of K in the presence of alkalosis. It seems to me that it is possible to consider that the secretion of K and H in Berliner's experiments may be independent phenomena, that there does not necessarily have to be a competition between K and H in the ion exchange in the renal tubular cells. There may be a competition that extends farther back than carbonic anhydrase, in which the materials that the cells liberate in the tissues is the controlling factor. This seems to have been true in Earle's case. That is a different kind of competition. As I pointed out, to me the quantitative evidence essential for Berliner's theory in the experiments he cited was not satisfactory. These experiments were the only ones available to me.

DR. PETERS: In answer to Dr. Visscher, who cited experiments in which, by perfusion of the renal portal

circulation of the frog, secretion of Na by the tubules had been demonstrated. Perhaps, my discussion was purposefully more or less provocative. If, by perfusion of the renal portal system, it has been demonstrated that the renal tubules do excrete Na, and if this is relevant to the mammalian kidney, the fact will have to be accepted. The fact will remain that it has been impossible to demonstrate it as yet and, for reasons that I mentioned, it will remain undetectable. So far as the net exchange of Na is concerned, therefore, it may as well be treated as nonexistent. What I really wanted to emphasize was the fact that it is improper to consider an ion exchange between Na and K in terms of K and K excretion only. It must serve also as a mechanism for the reabsorption of Na. To Dr. Mudge I apologize. I was trying to bring out the implications of his studies toward the secretion of Na. I realize that he was not trying to study excretion with his kidney slices.

DR. SCHWARTZ: In one case of chronic K depletion studied by Dr. Arnold Relman and myself, urinary K excretion was as low as 3 mEq. per day while the patient was on a normal K intake. An interesting feature of this case was the transient development of marked hyperkalemia due to persistence of low urinary K excretion. This patient and others with chronic depletion that we have studied had evidence of impaired renal function.

The evidence for depletion in these patients was that on a normal diet they retained 10 to 12 mEq. of K per kg. of body weight daily before they came into balance.

DR. RUBIN: Did you say they had depleted the body supply?

DR. SCHWARTZ: Evidence for depletion was that these patients, when put on a normal diet, retained 33 and the other 37 per cent of the ingested K. We have direct evidence from repletion that they had lost one-third of the total body K.

DR. BUTLER: How could you tell when the depletion had taken place?

DR. SCHWARTZ: We also studied this point and about 15 or 16 balances were run during steroid administration and with NH_4Cl, carrying out various maneuvers and also the changes in extracellular K. In none of these cases could we find a good correlation. We have had many cases in which serum K was normal and the electrocardiogram might or might not be normal. We hesitate to set up any rule on the relation between the two as it just don't hold. In one case electrocardiograms became normal very early while the K was severely depleted, and in the other, the reverse happened.

DR. DARROW: I would like to comment on this as I would think the correlation would be with the relation of H across the membrane because your concentration of K inside is going to be relatively high with reference to the K outside. In any case, it would be a disturbance in relation to the pH on the outside of the cells and the K adjusted to that. I don't think it would correlate with the degree of intracellular K.

DR. MC QUARRIE: I would like to ask Dr. Tarail about these interesting cases of nephritis in which there is hypopotassemia. What studies have been made of the ammonium function of the kidney?

DR. TARAIL: I would like to say a loud "amen" to what Dr. Schwartz has said in some detail. In fact he has, in large part, answered the questions that were directed to me.

I would say in supplementation that Forman recently studied normal subjects (Forman, I believe, is at the University of Oxford), and he studied normal subjects who received large quantities of ion exchange resins—which I suppose renders them abnormal, since they develop acidosis and other complications—and after about 8 or 9 days of administration of this resin, which swept out large quantities of K in stool and large quantities of K in the urine, there was a precipitous fall of excretion of K, with the concentration ratio falling to levels far below one of the subjects. (P.F., I suppose, stands for Forman.) The excretion rate in milliequivalents in 24 hours was something like two-tenths of a milliequivalent. So that was pretty good.

In addition, Dr. Schwartz pointed out, we have seen patients who, during phases of rehydration and reestablishment of normal carbohydrate and protein metabolism and metabolic stages, despite the fact there is little K in the fluid prescription, may occasionally excrete precious little K — much as Forman's normal subjects did.

With respect to your point of having administered the equivalent of the negative balance of K, ten milliequivalents in a normal subject, without being able to create a positive balance, I certainly would have no explanation, other than to wonder whether the metabolic state were not right. (That is a term I am probably using loosely, but we know that patients with diabetic acidosis have extremely rapid excretion rates of K, usually, initially.) In the diabetic acidosis it is quite high, but I doubt whether, if we gave K in diabetic acidosis in the face of a high concentration of urine K, we could get the cells to take it up because the metabolic wheel is going the wrong way. Carbohydrate metabolism, protein metabolism and water metabolism are all in a negative and unfortunate state, so to speak.

With respect to Dr. McQuarrie's query, I would say that I have no personal experience in studying the NH_4 problem. That is the question which dealt with the role of NH_4 formation in hypopotassemia. Apparently Albright, and some others, have good evidence to support the hypothesis that there is defective formation of ammonium with a wastage not only of K but of other cations as well, particularly Ca, and in some instances, Na.

. . . Initially, in diabetic acidosis before any therapy is given (salt replacement, etc.), before things are going well, the patient with diabetic acidosis may have elevated concentrations of serum K or normal concentration loss. The importance is, when carbohydrate metabolism is going the wrong way, early, before insulin action is taking effect, when rehydration has not been reestablished, preferably by other means than glucose solution, I would not expect K to be taken up because the fact of the matter is, the K is being lost from the cells at a very rapid rate.

I do think the only possible exception to that rather inferential reasoning is a situation in which initially the serum K is low in a patient, which may occur, particularly in children. Certainly, in most adults, under the circumstances I have mentioned, I think the administration of K would be unwise and we don't use it.

DR. KEITH: Just one point I would like to speak about in regard to Dr. Berliner's work with reference to the H ion concentration of the urine after the ingestion of K salts. A group of us in 1937 reported (Am. J. Physiol. 119:347:1937) some experiments in which we ingested large doses of different K salts on an empty stomach in the morning, and tested the urine hourly for the next eight hours. After $KHCO_3$ the pH of the urine soon became alkaline, registering a pH of 7.9, and this concen-

tration continued for 6 to 8 hours. With KCl the pH did not rise as high, to 7.7, and only persisted for 3 to 4 hours. Potassium nitrate caused an initial shift of pH to 7.1, but in 4 hours it had decreased to a pH of 5.0. The results with KCl and KNO_3 suggest that the kidney was excreting the anions and K in varying proportions during different periods of the experiment.

In answer to Dr. Butler with regard to the giving of K salts in hypopotassemia, Dr. Darrow pointed out the importance of not making up our minds to administer definite calculated amounts. We prefer to give the amounts necessary to restore the electrocardiogram or the serum K concentration to normal if disturbed, or to improve the symptoms of the patient. I should also like to say that, in order to recognize hypo or hyperpotassemia in the electrocardiogram, it is the sequence of the electrocardiographic tracings that is important and not a single tracing. This latter point has been emphasized by Dr. Peters.

DR. BUTLER: You took 12 grams of KCl on an empty stomach? I am very anxious to know if you had gastrointestinal cramps.

DR. KEITH: Last year the Turkish investigators, Berker, Metrani and Ulutin reported some effects of the ingestion of a solution of K phosphate, containing 20 gm. of K. One of the interesting results of their experiments was that tetany sometimes developed, but without any change in the concentration of serum calcium. However, there was a definite alteration in the ratio of Ca to K in the serum.

DR. BUTLER: Dr. Tarail says he supposes that in diabetic acidosis with the homeostatic mechanisms set to accomplish a large excretion of K there isn't any use of giving K early in the treatment of the patient. Such a supposition might lead to a delay in instituting K therapy that could get one into quite a jam; for continuing NaCl therapy would cause continuing excretion of K. Thus the longer you put off K therapy the harder time you are going to have correcting the K deficit.

Relationship of Potassium and Inorganic Phosphorus to Organic Acid Soluble Phosphates in Erythrocytes

Metabolic Effects of Acidosis

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THE organic acid-soluble phosphorus (OASP) compounds of blood cells serve diverse functions: in carbohydrate metabolism, being continuously synthesized and broken down through reactions of the glycolytic cycle; in the electrolyte equilibrium of the blood, as non-diffusible intracellular anions which undergo large changes in concentration under different pathologic conditions.[1] Gross changes in concentration of the total OASP in blood cells in a number of different conditions have been accounted for mainly in the diphosphoglycerate fraction: *decreasing* in acidotic states such as occur with gastroenteritis in infants, in diabetic ketoacidosis, and in experimental NH_4Cl acidosis; *increasing* with impairment or suppression of renal excretion of waste phosphates, and after pyloric obstruction and vomiting, with hypochloremic alkalosis. Under such conditions of acidosis and alkalosis a reciprocal relationship between changes in the concentrations of intracellular Cl and of OASP may be observed. With diabetic ketoacidosis changes in concentrations of OASP and of K in the blood cells are closely parallel, decreasing with the development of acidosis and increasing together during recovery.[2,3] Observations made in a variety of clinical and experimental studies suggest that changes in concentration of the OASP and of K in the blood cells may serve as valuable indices of the state of the labile stores of P and K in other body tissues.

Other investigators also have found the turnover of K in blood cells to be intimately linked with the metabolism of these P compounds. Hastings and coworkers have shown that there is a constant dynamic interchange of K in human red cells and that the maintenance of the K gradient between cells and plasma is dependent on glucose metabolism.[4,5] The metabolism of glucose is of course linked with processes of phosphorylation of other intermediary compounds.

Metabolic balance studies on alloxan-diabetic rats[6] yielded indirect evidence of the large losses of labile intracellular constituents, especially N, P and K, confirming and amplifying observations on human subjects reported by others. This indirect evidence has been amplified further by direct analysis of tissues. In the muscles of alloxan-diabetic rats with severe ketoacidosis, compared with normal controls, the concentrations of H_2O and K decreased, the concentration of N increased slightly, with values for Na and Cl showing no significant change relative to the total solids. The higher than normal N content suggested that acidosis led to greater losses of non-protein constituents than of protein from the tissue cells. In the erythrocytes, the average concentration of K was reduced from 109 mEq./l. in the normal controls to 89 mEq./l. in the rats with ketoacidosis, corresponding to reductions of erythrocyte K found in human patients with diabetic acidosis. Further studies on the OASP in tissues are in progress.

Our studies on interrelationships between the metabolism of glucose, K and P have included insulin

sensitivity tests done on normal and alloxan-diabetic dogs, in nonacidotic states and in states of severe acidosis induced by slow intravenous perfusion of NH_4Cl M/6 solution. This procedure was chosen for producing a nonketonemic type of acidosis the effect of which could be studied apart from complex factors involved in diabetic acidosis. The acidosis thus induced was characterized by a fairly constant pattern of chemical changes in the blood: decreased serum pH and CO_2 content, hemoconcentration, a moderate increase in blood sugar (average fasting levels increased from 74 to 99 mg/100 cc.), hyperchloremia, and a decrease in concentration of the OASP in the cells comparable to the decreases found in the blood of patients in diabetic acidosis. For the insulin sensitivity tests parallel determinations of blood sugar, plasma K and inorganic P were made before and at intervals during 3 hours after the intravenous injection of standard doses of insulin (see fig. 1).

In acidotic dogs standard doses of insulin produced less fall in the concentration of blood sugar, with slower rate of fall and slower recovery, than in the same dogs in nonacidotic states. In nonacidotic dogs the concentrations of plasma K and inorganic P decreased sharply and then returned to normal within the 3-hour period after insulin, closely parallel to changes of the blood sugar; but in the acidotic dogs after insulin the levels of plasma K and inorganic P tended to change very little or to remain stationary.[7,8] Thus, acidosis appears to inhibit the action of insulin by interfering with processes of phosphorylation that are involved in the concomitant cellular uptake of sugar, K and P from the blood plasma.

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CHAIRMAN ANDERSON: Discussion of this paper will be deferred until the presentation of the papers of Dr. Gardner and Dr. Teng.

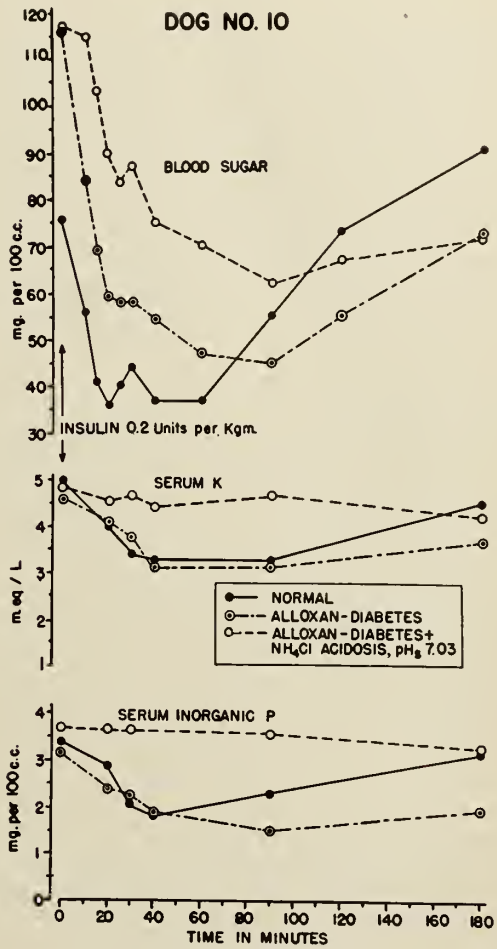

Fig. 1. Insulin-sensitivity tests in a dog before and after diabetes was induced by alloxan, and in the alloxan-diabetic dog in severe acidosis induced by intravenous perfusion of NH_4Cl solution.[8]

Experimental Potassium Depletion

Effect on Carbohydrate Metabolism and pH of Muscle

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Recent years have seen a rapid acquisition of knowledge concerning the repair and maintenance of intracellular as well as extracellular fluid. Evidence suggesting deficiency of intracellular K has been found in patients who have become depleted as a result of diarrhea, chronic sprue, ulcerative colitis, loss of fluid from the gastrointestinal tract by vomiting or drainage, diabetes mellitus, Cushing's syndrome, excessive therapy with intravenous NaCl and excessive therapy with cortisone or desoxycorticosterone.[1] Rational treatment of intracellular electrolyte depletion demands a more adequate understanding of the organic and inorganic composition of intracellular fluid. In an effort to gain information about the effects of chronic K deficiency on carbohydrate metabolism and pH of skeletal muscle, the following experiments were carried out. The original data have been published in detail elsewhere.[1–3]

A. *Effects on carbohydrate metabolism*

The effects of severe K deficiency on the metabolism of glucose and glycogen in intact rats weighing 160 to 175 g. were examined. This condition was produced by a synthetic diet containing 0.07 mM. K per 100 g. body weight and 30.4 mM. Na per 100 g. The diet was fed to rats weighing 160 to 175 g.

Rats kept on the K-deficient diet for 40 to 60 days showed abnormally high postprandial liver and muscle glycogen concentrations, normal fasting blood glucose and urine glucose concentrations, normal oral glucose tolerance curves, moderately diminished circulating eosinophils and enlarged adrenal glands.

Rats kept on the K-deficient diet 90 to 120 days showed low to unmeasurable postprandial liver and muscle glycogen concentrations, markedly elevated oral glucose tolerance curves, few or no circulating eosinophils and enlarged adrenal glands.

The results obtained indicated that chronic K deficiency in the intact animal has dual effects on carbohydrate metabolism. One effect becomes evident relatively early and is associated with abnormally high concentrations of liver and muscle glycogen (see figure 1). This may be due to an increased secretion of adrenal carbohydrate-active steroid, since the animals at this time showed increased adrenal weights and low total eosinophil counts (figures 1 and 2). When the animals were further depleted of K, there developed diabetic glucose tolerance curves and an almost total absence of liver and muscle glycogen (figures 1 and 3). These findings suggest that in K deficiency there is a defect in intracellular fluid which prevents glycogenesis.

Subsequent clinical studies by Eliel, Pearson and White have demonstrated similar findings in patients suffering from postoperative K deficit.[4] These workers found that whereas their patients had normal glucose tolerance tests preoperatively, postopera-

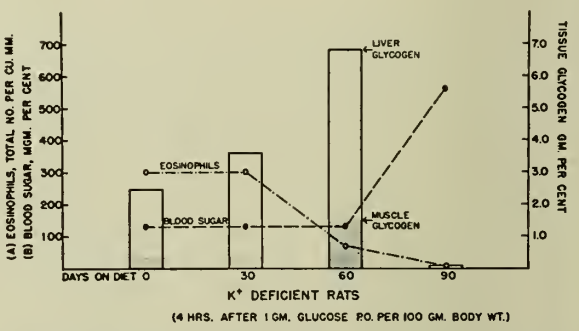

Fig. 1. Composite diagram illustrating relationships between concentrations of liver and muscle glycogen, blood sugar, and total circulating eosinophils in control and K-deficient rats.

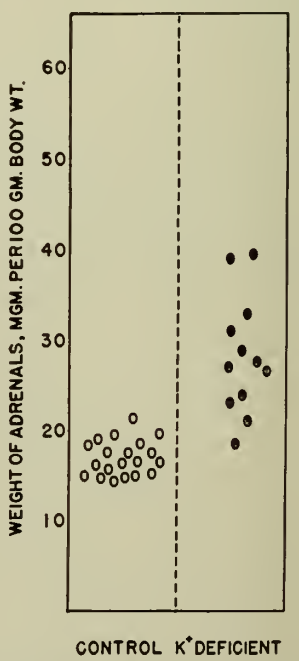

Fig. 2. Comparison of adrenal weights in control rats and K-deficient rats.

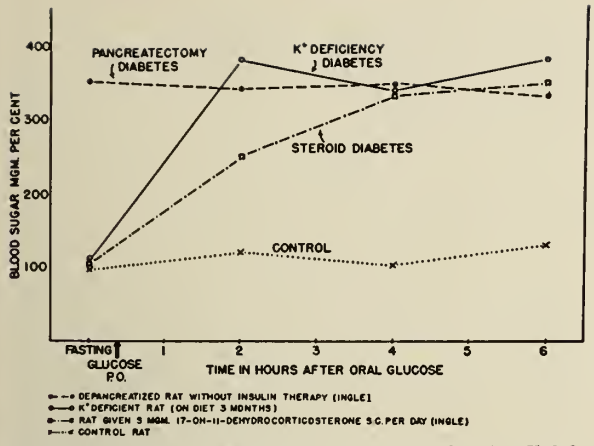

Fig. 3. Oral glucose tolerance curves in a control and a K-deficient rat compared with glucose tolerance curves done by D. J. Ingle and colleagues (Endocrinology) on a depancreatized rat and on a rat injected with cortisone.

tively there developed gradually increasing glycosuria correlated directly with the cumulative postoperative intracellular K deficit.

B. *Effects on H ion concentration of cell fluid*

In 1937 McQuarrie, Johnson, and Ziegler discovered that a patient with hyperadrenocorticism (Cushing's type) exhibited low serum K and Cl concentrations and increased serum pH and carbon dioxide concentration.[5] Two years after this observation Heppel reported that dietary K deficiency in rats was associated with low serum Cl Values.[6] Later Orent-Keiles and McCollum found that rats maintained on a low K diet excreted much more Cl than did the controls.[7]

In 1948 the observations of Darrow and colleagues[8] and Locke and colleagues[9] defined the direct relationship between intracellular K deficiency and extracellular hypochloremic alkalosis.

The enigmatic behavior of extracellular Cl and bicarbonate under the foregoing circumstances stimulated the present author and his colleagues to investigate the intracellular concentrations of the H and bicarbonate ions in K deficiency.[2,3]

The technique of determining intracellular H ion concentration in mammalian muscle, as described by Wallace and Hastings, was used.[10] These calculations depend upon the validity of two assumptions: (1) that the Cl ion does not enter muscle cells, and (2) that most of the total muscle CO_2 exists as the HCO_3^- ion. This problem has been reviewed critically by Conway and Fearon.[11] Such data were obtained from a group of rats made K deficient over a period of 40 days (see table 1). These animals developed severe hypochloremic alkalosis in confirmation of previous observations. The intracellular pH of the skeletal muscle of the controls was found to be 6.98± 0.08*. There was an increase in the serum partial pressure of carbon dioxide (pCO_2) in the K deficient rats together with increases in concentrations of $H_2CO_3^-$ per kg. extracellular water and H_2CO_3 and inorganic phosphate per kg. intracellular water. There was a decrease in concentration of CO_2 and HCO_3^- per kg. intracellular water. There was evidence for a considerable movement of H ions into the cell in K deficiency, since intracellular pH was found to be 6.42 ± 0.05.

*± = Standard error of the mean.

TABLE 1
DERIVED DATA FROM RAT SERUM AND SKELETAL MUSCLE

Group	No. of rats	pCO_2	[Cl]s	[Cl]e	$(H_2O)e$	$[H_2CO_3]e$	$[HCO_3]s$
		mm. Hg	M.eq.per kg. H_2O	M.eq.per kg. H_2O	gm. per kg.tissue	mm. per kg. H_2O	M.eq.per kg. H_2O
Control	5	42.4	96.9	102.0	144.6	1.28	26.8
S.E.		2.3	1.4	1.5	12.5	0.11	0.9
K-deficient	6	52.4†	83.2†	87.4‡	147.8	1.67	42.06‡
S.E.		1.9	1.9	1.7	15.6	0.05	1.7

Group	No. of rats	$[HCO_3]e$	$(CO_2)e$	$[CO_2]e$	$[H_2CO_3]e$	$[HCO_3]e$	pHe
		M.eq.per kg. H_2O	Mm. per kg.tissue	Mm per kg. H_2O	Mm.per kg. H_2O	M.eq. per kg. H_2O	
Control	5	28.2	7.7	12.66	1.41	11.24	6.98
S.E.		1.0	1.02	1.50	0.15	1.49	0.08
K-deficient	6	44.2‡	4.13*	6.90*	1.83*	5.05†	6.42‡
S.E.		1.8	0.80	1.52	0.10	1.31	0.05

Data were derived by the Wallace-Hastings calculation. Parentheses designate concentration per kilogram of serum, extracellular or intracellular phase, and whole tissue. Brackets designate concentration per kilogram of water of the particular compartment. Serum, extracellular and intracellular phases are referred to by the subscripts s, e, and c respectively.

S.E. — standard error of the mean.

Figures marked with asterisks differ significantly from values of corresponding control groups: P = 0.05-0.02 (*); P = 0.02-0.001 (†); P = less than or equal to 0.001 (‡).

From these observations, it would appear that diminution of intracellular K concentration demands that a new "abnormal" equilibrium of electrolytes be established on both sides of the cell membrane. This new equilibrium involves not only an extracellular hypochloremic alkalosis, but also an intracellular increase of H and inorganic phosphate ions and decrease of bicarbonate ions.

SUMMARY

Rats deprived of K over long periods of time develop an abnormal carbohydrate metabolism, characterized by postprandial hyperglycemia and inhibited tissue glycogenesis. These animals show an increase of intracellular concentration of H and inorganic phosphate ions. The latter findings may be the result of rearranged ionic equilibria on both sides of the cell membrane.

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Effect of Potassium Ions and Other Electrolytes on Carbohydrate Metabolism in Liver Slices

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THE IMPORTANCE of K and Na ions for the synthesis of glycogen by liver slices *in vitro* has been well documented.[1-3] The purpose of the present investigation was twofold. First, to find a medium of suitable cationic composition in which synthesis from pyruvate could be regularly obtained. Second, to provide information on how and where do K and Na ions act to influence the reactions of carbohydrate metabolism, of which glycogen synthesis is but one aspect.

In the first series of experiments, using non-isotopic glucose or pyruvate as substrate, we have compared the synthesis of glycogen in six media containing different concentrations of the cations, K, Na, Mg and Ca. It was found that a medium containing K, Mg and Ca at the respective concentration of 110, 20 and 10 mM/1 was the best of the six. In this medium rat liver slices synthesized glycogen from pyruvate as well as from glucose. The replacement of half of the K ions by equivalent amount of Na ions resulted in less glycogen formation; the presence of both Mg and Ca ions was more effective than the presence of either one alone.

Having found an effective medium, the study of the effect of K and Na ions was extended to other aspects of carbohydrate metabolism in a second series of experiments. Using C^{14} labeled glucose and C^{14} labeled pyruvate as substrates, simultaneous measurements of the uptake of labeled glucose and of labeled pyruvate, the formation of new glucose from labeled pyruvate as well as the synthesis of glycogen from the labeled substrates were carried out. In the study, comparisons were made among three media having identical concentrations of Mg (20 mM/1) and Ca ions (10 mM/1) but different concentrations of K and Na ions: Medium 1: K 110, Na 0; Medium 2: K 40, Na 70; Medium 3: K 5, Na 105 mM/1. The detailed experimental procedures and methods for calculation have been reported elsewhere.[4] In each experiment, two flasks were employed, one containing labeled glucose and unlabeled pyruvate, the other unlabeled glucose and labeled pyruvate. Except for the differential labeling of the substrates, the twin flasks were duplicates in all other respects. The liver slices were analyzed for glycogen and the medium for glucose, pyruvate, CO_2 and lactic acid, chemically and isotopically, at zero and/or final time. From the average chemical data and the two sets of isotopic data—namely, from flask 1, the specific activities of the substrate C^{14} glucose, the final glucose, final glycogen and final CO_2; and from flask 2, the specific activities of the substrate C^{14} pyruvate, the final glucose, final glycogen and final CO_2 it was possible to derive data on glucose uptake, glucose formation from pyruvate as well as glycogen synthesis and CO_2 production from the added glucose and pyruvate. The results of these experiments are summarized in table 1.

TABLE I
EFFECT OF K AND NA IONS ON CLYCOGEN AND GLUCOSE METABOLISM IN LIVER SLICES IN VITRO
(All results expressed in micromoles of glucose per g. of wet liver per 90 minutes)

		Medium 1	*Medium 2*	*Medium 3*
Glycogen,	initial	5.9	9.6	7.3
	final	25.9	14.4	6.1
	net change	20.0	5.4	−1.2
	from glucose	11.5	4.2	2.0
	from pyruvate	9.7	5.6	2.5
Glucose,	uptake	36.5	25.6	17.0
	from pyruvate	15.6	23.2	26.4

It is seen that a large net increase of glycogen occurred in Medium 1. Much less was found in Medium 2. With Medium 3 a net loss of glycogen was observed. Similar relationships were obtained in the amounts of glycogen synthesized from glucose and pyruvate. These total 21.2, 9.8, and 4.5 μM/g. in Medium 1, 2, and 3, respectively. If these figures are taken as the amounts of new glycogen formed, one may calculate the amounts of glycogen breakdown as follows:

Glycogen breakdown = (initial glycogen)−((final glycogen)−(new glycogen)).

By substituting the values shown in table 1, one obtains 1.2, 4.4, and 5.7 μM/gm. as the amounts of glycogenolysis in Medium 1, 2, and 3, respectively. These results therefore indicate that K ions both promote glycogen synthesis and inhibit glycogen breakdown, whereas Na ions promote glycogen breakdown as well as retard glycogen formation.

From table 1 it is also seen that the uptake of glucose is progressively reduced as the proportion of K ions to Na ions in the medium is decreased. Conversely, glucose production from pyruvate is increased with increasing Na ion concentration in the medium.

The effect of K and Na ions on the uptake of pyruvate and the oxidation of labeled glucose and pyruvate to CO_2 was negligible. Somewhat more lactic acid was found in media with higher Na ion concentrations.

Under quite similar experimental conditions, Flink, Hastings and Lowry[5] have studied the changes in K and Na concentrations in rat liver slices incubated in media with varying concentrations of these ions. They have come to the conclusion that the concentration of K ions in the incubation medium required to maintain a normal intracellular K concentration of liver slices during incubation appears to be about 38 mM/l, and that, with an extracellular K concentration of less than 5 mM/l., the intracellular K concentration decreases markedly and irreversibly. These critical concentrations of K ions are close to those employed in Medium 2 and 3 of the present experiments. The differences in the results as summarized above may therefore be ascribed to the changes of the intracellular K concentration in the liver slices incident to incubation.

From the data presented, it appears clear that more than one of the intermediary steps of carbohydrate metabolism are affected by K and Na ions, and that these ions exert opposite effects on the same processes. Although the exact manner by which the ions act on the enzymatic reactions involved has not been identified in the liver slice system, it is felt that the present observations give additional support to the hypothesis that the maintenance of a normal intracellular ionic environment is essential for the normal metabolic activity of the liver cells.

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DISCUSSION

DR. FENN: I should like to comment on a point in Dr. Gardner's paper which relates to the measurement of the H ion concentration inside the cells by the application of the Henderson-Hasselbalch equation. In using this method Conway subtracted the carbamino CO_2 from the total CO_2 content as Dr. Gardner pointed out. After making this correction he obtained a pH inside the muscle which agreed with his theoretical expectations. Without this correction the inside solution has too low a H ion concentration for its high K concentration. When CO_2 combines with the NH_2 group to form a carbamino compound, it liberates a H ion just as it does when it combines with OH_2 to form bicarbonate. Both H ions have to be buffered in the same way. Until we know the pK value for the carbamino compound, we cannot be sure that this correction is justified. In calculating the pH of the plasma from the bicarbonate and the pCO_2, we do not make a correction for the small amount of carbamino CO_2 present, presumably because the pK value has been determined on the assumption that all the combined CO_2 is bicarbonate.

While I am on my feet, may I comment on Dr. Teng's paper in which he explains the effect of K on glycogen deposition in terms of the increase in the K concentration inside the cell. While this is certainly the simplest and most reasonable interpretation, I should like to suggest the possibility that the result might be due to a stimulation of carbohydrate metabolism at the cell surface by the high K concentration outside the cell. I say this because of experiments of Rothstein at the University of Rochester, who has found that K stimulates the anaerobic and aerobic metabolism of yeast cells in quite acid solutions. It is the K concentration outside which determines this stimulation, not the amount of K uptake, nor the concentration of K inside. He found also that the K outside is in competition with the H ion. If there is more H ion concentration outside, more K is required for the same stimulation. Now your K seems to be (figure 1 and also figure 1 page 163) in competition with Na, but is it in competition with the H ion also? Have you tested whether in a more acid medium more K is needed to produce the same increase in glucose uptake and glycogen formation?

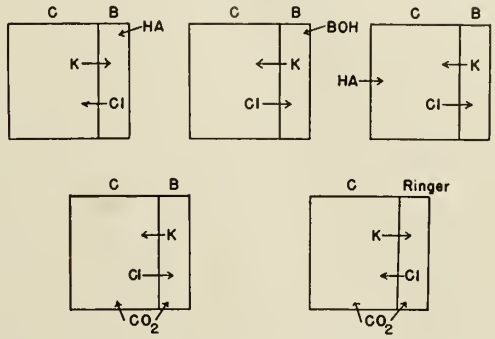

Fig. 1. Diagram illustrating the expected movements of K and Cl ions between tissue cells (C) and blood (B, including the erythrocytes) or Ringer's solution. Fixed acid (HA) or base (BOH) or high CO_2 is supposed to be added to one or both of the phases as indicated and the resulting movements of K and Cl are shown by arrows. The indicated movements of K have been demonstrated on frog muscles but the changes in Cl are largely hypothetical.

DR. DARROW: Dr. Gardner, I am anxious to know at what stage in your experiments with alkalosis of K deficiency you determined the bicarbonate determinations. We did some without nearly as marked alkalosis of K deficiency as that shown in your slide and did not find any change in the muscle bicarbonate, or rather the total muscle CO_2 which is a better term for your determination.

DR. HOWARD: I would like to ask Dr. Guest a practical question in regard to the necessity of or advantage of administration of inorganic phosphate along with K and, of course, glucose during recovery from diabetic acidosis. When we have given amino acids, K and PO_4 together, the uptake of K by the cellular compartment was much greater than that of either N or P; the latter two lagged and were accepted in about their relative proportions in normal muscle. So, we do not use phosphate ordinarily. Also, an experience comes to mind in which I had to give a steatorrheic patient large amounts of Ca orally to keep her out of tetany. Serum P was made very low, of course, and for a month remained less than 1 mg. per cent. Yet, during this time we could detect no abnormality of carbohydrate metabolism as judged by fasting blood sugar or glucose tolerance tests. Neither Dr. Hastings nor Dr. Cori were astonished when I mentioned this to them; and as I recall it, both felt that carbohydrate metabolism would go on perfectly all right with but very small quantities or inorganic phosphate present. So do you think it wise to give phosphate or do you give it to your patients routinely during their emergence from diabetic acidosis?

DR. WILDE: First of all I wish to congratulate Dr. Guest upon the extensiveness of his data and on studying a preparation that seems to yield information not only of fundamental but also of practical import.

I wonder in connection with the studies on dog erythrocytes whether the Na exchanges were followed. In electrolyte studies we often pose the question whether during biochemical changes nonspecific cation shifts occur merely to satisfy the electrostatic charges set up by newly synthesized anions or whether the biochemical machinery has specific effects on Na or K transport mechanisms. In your system, it would be interesting to learn whether Na in a Na-rich dog erythrocyte behaves as does K in a K-rich erythrocyte.

Further, did you make an ionic balance sheet? How does the sum of total anion changes compare to the sum of cation changes?

DR. FLINK: I would like to clarify something about the slide that Dr. Teng showed. It is unlikely that the K concentration inside the cell in terms of mEq./liter of cell water increased beyond the concentration outside the cell. The representation in terms of dry weight of tissue must mean that there is cell swelling in high K media. As a matter of fact wet weight determinations indicated just that. Perhaps this might explain to some extent the increased glucose uptake, for if water has to go into the cell, glucose and other substrate might go into the cell too.

DR. PHILLIPS: I would like to ask Dr. Guest if he has followed the Ca story in his experimental animals. I do this for one reason because we have become quite interested in arthritis and are attempting to produce it in laboratory animals. This was stimulated by an experience of E. B. Hart, who became arthritic and went back in his own research experience to some work he had done with swine about 1910 where he fed NH_4Cl and succeeded in reducing the Ca-P in the bones. He thought that with the development of arthritis in his own case he might be able to take out the excess Ca and P by the administration of NH_4Cl. I don't know what the physicians recommend for therapeutic doses of NH_4Cl but Prof. Hart took 5 grams per day for 21 days. Pain was relieved and he was able to walk erect again. He has taken the second course of what he calls "polishing his bones" by the voluntary intake of 5 grams of NH_4Cl a day. I asked him if he weighed out each pellet of NH_4Cl and he said no he just took a teaspoon and leveled it off with his finger. I quickly went to the laboratory and did the same thing and found that I had 7 grams instead of 5. So I am sure he had at least 5 grams per day and in his case and in several other cases among his friends it has worked. I wondered if there was any information on that point.

DR. BUTLER: For the record, hadn't we better say that the clinicians present didn't endorse this therapy until further studies had been made concerning what it really did?

DR. PHILLIPS: I was about to suggest that we have another symposium on that point.

DR. TENG: The reason why we explained our findings on the basis of Dr. Flink's data was that they seemed to correlate and fit well with the thesis that normal enzymatic activities of the liver cells depend upon the maintenance of normal intracellular ionic environment. As a matter of fact, the express purpose of Dr. Flink's experiments was to show quantitatively the changes of intracellular K concentration of liver slices incident to incubation in media with varying concentrations of K and Na ions.

Dr. Fenn's comment offers an alternative explanation of how K in the medium may affect the metabolism inside the cell from outside. With regard to the question of competition between K and H ions, our experiments did not offer an answer, as the medium in our experiments was well buffered and the pH was maintained close to 7.4 throughout the incubation. Does that answer your question, Dr. Fenn?

DR. GARDNER: We are indebted to Dr. Fenn for his early work in investigating the CO_2 dissociation curve of frog muscle (Fenn: Am. J. Physiol. 85:207, 1929). I appreciate also, his comments on the carbamino problem, since it certainly is an important source of difficulty in interpreting the type of data that we get in attempting to estimate intracellular pH. Dr. Wallace, the new head of pediatrics at Western Reserve University, is also very much interested in elucidating that problem. In answer to Dr. Darrow, we did the muscle CO_2 determinations on animals that had been on the K deficient diet for approximately 40 days. Our values for acid-labile CO_2 on a wet weight basis were the same for both groups. The difference comes when one subtracts the very high values for extracellular CO_2 in the K deficient animals.

DR. GUEST: Dr. Howard's question regarding possible needs for phosphate in electrolyte repair therapy is indeed important. Certainly the body stores of P are greatly depleted during diabetic acidosis; the very slow restoration of organic P compounds within the blood cells and low excretion of P in the urine many days after apparent symptomatic recovery reflects this depletion. I do not know of any physiologic disturbances that can be definitely ascribed to P deficiency per se, under such circumstances. But, inasmuch as P metabolism is closely linked with that of carbohydrate and of K, it is likely that a lack of available P is related to derangements of K metabolism on which attention is focused in this symposium. We have presented some evidence that the administration of P salts (with Na and K) hastened the restoration of a normal electrolyte structure (including the organic phosphates) in blood cells (ref. 3). Dr. Butler and Dr. Darrow both have included phosphates

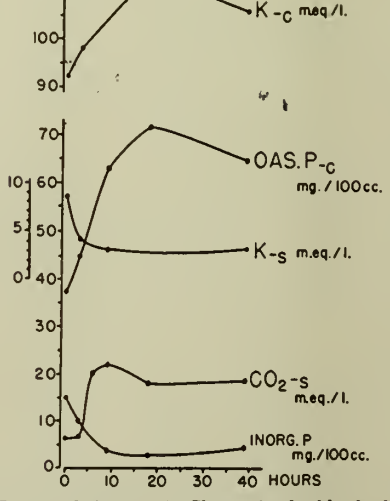

Fig. 2. (Guest and Rapoport) Change in the blood of a woman in coma, following treatment with insulin and intravenous fluids containing sodium and potassium phosphates.

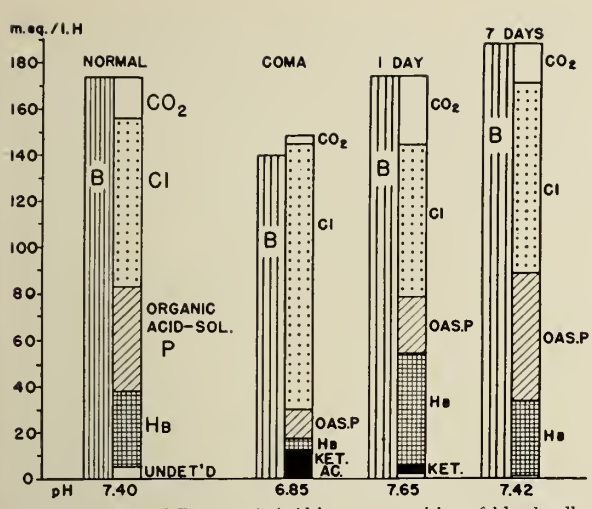

Fig. 3. (Guest and Rapoport) Acid-base composition of blood cells of a patient in coma with severe acidosis and on first and seventh days of recovery.

in their formulae for multielectrolyte solutions to be used in fluid repair therapy; but more quantitative data than are now available are needed for better definition of quantitative needs for phosphate in such therapy.

Replying to Dr. Wilde's query regarding the role of organic phosphates in the electrolyte structure of the blood cells, I should like to show here again a chart depicting gross changes in the cation-anion composition of blood cells in a patient studied in states of severe diabetic acidosis and during recovery (figure 3). Changes in "total base," with values low in the first sample and high in the last sample, are now known to be accounted for mainly by changes in concentration of K. In each sample, the sum of the calculated anion equivalents agreed closely with the determined total base. In the first sample the cell-Cl was high, the bicarbonate was low, the total organic phosphates low, with the diphosphoglycerate fraction practically zero, and ketone acids constituted an important part of the anions. In the second sample, with ketones nearly eliminated, the bicarbonate was high (after administration of $NaHCO_3$) and the organic phosphates were still low. Without changes in concentration of hemoglobin, the anion equivalency of hemoglobin does change markedly at different pH values, as shown in the chart. In the last sample, on the seventh day, the organic phosphates had risen to somewhat above the normal level; but on this day the urinary exeretion of P was still practically nil, reflecting the avidity of tissues retaining the available P, as mentioned previously. The urinary P excretion did not rise to normal until after the tenth day.

Replying to Dr. Phillip's question regarding changes of Ca, it may be said that it is well known that much Ca is lost in the urine in acidosis, paralleling losses of K and P, if renal function is not impaired. Many years ago Dr. M. A. Logan studied the effects of NH_4Cl acidosis on Ca excretion of rabbits. He found tremendous losses of Ca in the urine of the acidotie rabbits during periods of 7 to 10 days leading to demonstrable osteoporosis. But I doubt that doses of 5 to 7 grams of NH_4Cl in adult human subjects would lead to significant acidosis and to much depletion of Ca as a consequence. In the experiments done with Rapoport, previously mentioned (Guest and Rapoport[1,2]), doses of 25 grams a day in a normal human adult led to slow development of aeidosis, becoming severe after 4 or 5 days. These observations were comparable to the experience of Haldane reported many years ago. Doses of 5 to 7 grams might indeed lead to some increased acidity of the urine, and to some increased phosphaturia, but are not likely to produce a significant shift of pH and bicarbonate in the well-buffered blood. In the postacidotic period of recovery from severe diabetic acidosis, moderate degrees of hypocalcemia may be observed not infrequently, the result of avid uptake of Ca from the blood into the tissues. Mechanisms leading to such hypocalcemia are comparable to those that lead to hypopotassemia and hypophosphatemia, often observed in the postacidotic period.

The Role of Potassium and Related Cations in the Action of Pyruvic Phosphoferase and Other Enzymes

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A PROMINENT BIOCHEMICAL FUNCTION of the K^+ ion is its ability to activate certain enzyme reactions, as shown as early as 1937[1] and demonstrated for a specific enzyme reaction in 1942.[2] Enzyme reactions for which a pronounced K ion activation has been found include pyruvic phosphoferase,[2,3] phosphofructokinase,[4] fructokinase,[5] choline acetylase,[6] "malic enzyme,"[7] phosphotransacetylase,[8] aldehyde dehydrogenase,[9] and lactase.[10] In addition the reaction of ATP, acetate, and coenzyme A to give acetyl coenzyme A requires K ion.[11] Enzymes of the glycolytic sequence other than those mentioned apparently require little or no K^+. Optimum concentration of K^+ is usually quite high (e.g. 0.04 to 0.15 M), with inhibition at higher K^+ concentrations. For rabbit muscle pyruvic phosphoferase, K^+ has been demonstrated to be an essential activator with a Michaelis constant of 0.011M.[12] No consistent relation is apparent between the type of enzyme reaction and the K^+ requirement.

The K^+ activation of pyruvic phosphoferase appears to be a general phenomenon in animal tissues,[13] and may be demonstrated by colorimetric measurement of pyruvate formed with an assay system containing dilute filtrates of tissue extracts, phosphopyruvate, ADP, Mg^{++}, K^+, hexokinase, and glucose. K^+ activation is shown with enzyme preparations from rabbit skeletal muscle, heart, brain, uterus, liver, and kidney; with tissues from 10 widely different animal species which have been tested; and

with yeast and tetrahymena. The enzyme from fresh water mussels, which have low intracellular K^+ concentrations, requires lower K^+ concentrations for activation than the enzyme from marine forms or mammals.

Additional understanding of the mechanism of K^+ activation of pyruvic phosphoferase has been obtained by kinetic analysis based on equations describing enzyme systems requiring two substrates.[12] The experimentally measured Micahelis constants for K^+ (0.011 M) and phosphopyruvate (8.6×10^{-5} M) are independent of the concentration of the other component. These results and other data rule out formation of K^+-substrate compounds as an activation mechanism for this enzyme. The results are in harmony with independent combination of the K^+ and phosphopyruvate with the enzyme providing that the concentrations of the reactants are determined by the various equilibria involved. Alternately obligatory combination of one reactant may take place under "steady-state" conditions. Clearly the data show specific K^+ binding in preference to Na^+ by the enzyme. With aldehyde dehydrogenase the time lag for K^+ activation[9] suggests obligatory reaction of the enzyme with K^+ before reaction with substrate.

The incorporation of radioactive pyruvate-2-C^{14} into phosphopyruvate is catalyzed by pyruvic phosphoferase only in the presence of both K^+ and ATP in addition to other components of the reaction system.[13] The requirement of ATP for the exchange rules out the possibility that the reaction may proceed by formation of an enzyme-phosphate intermediate formed from the enzyme and phosphopyruvate independently from the combination with ADP. The rate of the reaction at equilibrium is only roughly 1/4,000 of the initial rate of phosphate transfer to ADP. On the basis of relative concentrations of the glycolytic enzymes in muscle, it is probable that the pyruvic phosphoferase reaction is the limiting step in the incorporation of pyruvate into glucose or glycogen.

The ammonium ion and Rb^+ can usually replace K^+ for the activation of pyruvic phosphoferase and for other K^+ requiring enzymes where they have been tested, while Na^+ and Li^+ are inhibitory to the K^+ activation. In appropriate assay systems Na^+ can activate the enzyme approximately 7 per cent and Li^+ approximately 0.6 per cent as much as K^+. Likewise the activity of yeast aldehyde dehydrogenase in presence of Na^+ is 4 per cent of that with K^+.[9] Pyruvic phosphoferase is strongly inhibited by Ca^{++}. Kinetic experiments show that the inhibition by Ca^{++}, while in part overcome by additional K^+, is not a simple competitive inhibition. Likewise the weaker Na^+ and Li^+ inhibitions of pyruvic phosphoferase[2,3,13] and aldehyde dehydrogenase[9] do not appear to be competitive.

The activation of enzymes by K^+, NH_4^+, and Rb^+ suggests that properties which these ions have in common are associated with the activation. These ions have similar and smaller hydrated ionic radii and similar and larger crystal lattice radii than Na^+ or Li^+, and likewise show similar polarizability and ionic potential. Enzymes showing K^+ activation may have a negatively charged site which will combine with K^+ much more strongly than with Na^+. Alternatively the enzyme combined with Na^+ may be inactive, possibly due to the extent of geometric displacement associated with the combination. The reasons why the binding of K^+ or a closely related cation is essential for catalytic activity are problems for the future.

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See discussion following Dr. VON Korff's paper.

The Effect of Alkali Metal Ions on Acetate Activation by an Enzyme from Heart Muscle* †

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The key position of acetyl coenzyme A in intermediary metabolism has been established by numerous recent investigations[1–8] (see figure 1). The formation of acetyl choline from acetate, ATP, CoA, and choline has been reported by Nachmansohn and colleagues to be stimulated by K^+[5] and inhibited by Na^+[5a]. At least two enzymatic reactions are involved in choline acetylation thus preventing a decision as to the site(s) of action of the ions.

*The following abbreviations are employed in this abstract: ATP, adenosine triphosphate; CoA, coenzyme A; AcCoA, acetyl coenzyme A; AMP, adenosine-5-phosphate; PP*i*, inorganic pyrophosphate; P*i*, inorganic phosphate; As*i*, inorganic arsenate; AcP, acetyl phosphate.

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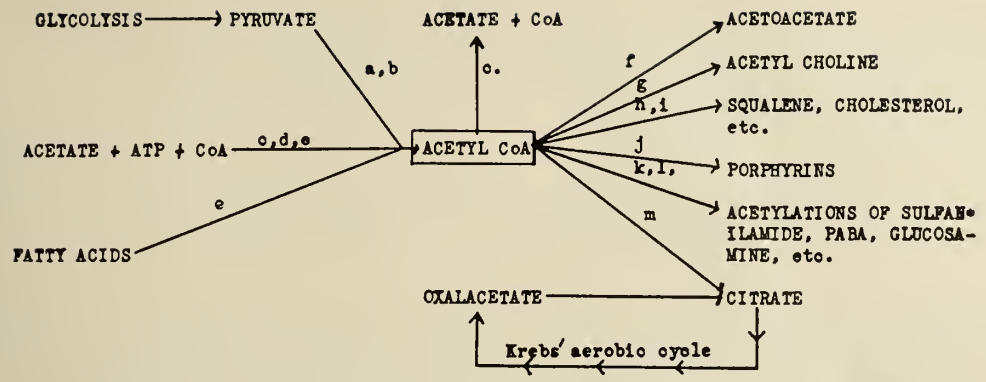

Fig. 1. Diagrammatic representation of the key position of acetate metabolism in animal organisms.††

In the present work, conversion of acetate ion to the high energy intermediate acetyl-CoA[9] catalyzed by a soluble enzyme from heart[8] has been shown to be stimulated by K, NH_4 or Rb ions and to be inhibited by Na or Li ions.

The reactions involved in the test system are:

(a) $AcO^- + ATP + CoA \rightarrow AcCoA + AMP + PPi$ [10,11]

(b) $AcCoA + NH_2OH \rightarrow AcNHOH + CoA$

Reaction (a) is a physiological reaction catalyzed by the heart enzyme. Reaction (b) is believed to be nonenzymatic.[12] The acethydroxamic acid formed is determined colorimetrically by a modification of the Lipmann and Tuttle procedure.[13]

Preliminary experiments have indicated that when the acetate activating process is coupled with the condensing enzyme system of Ochoa and co-workers[14] the synthesis of citrate is increased by K and decreased by Na.

Stimulation of reaction (a) by K, NH_4, or Rb ions is maximal at a concentration of about 50 mM. Inhibition of reaction (a) by Na is about 50 per cent at a concentration of 20 mM.

The effects of the alkali metal ions on the process of acetate activation are qualitatively and quantitatively similar to those reported by Stadtman[15] for the bacterial enzyme phosphotransacetylase which catalyses reaction (c).

$$\text{(c) } AcP + CoA \rightarrow (AcCoA) + Pi \xrightarrow[As\,i]{H_2O} AcO^- + CoA$$

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DISCUSSION

DR. GARDNER: Dr. Boyer mentioned that cephalin binds with K. Some years ago, Dr. Réné Dubos found that gramicidin binds rather specifically with cephalin. It would be interesting to know if gramicidin and K would compete for cephalin. Has any work been done on this? I would like to ask Dr. VON Korff if he subscribes to Dr. Fritz Lipmann's hypothesis that two-carbon fragments are the precursors of the steroid nucleus and form its structure by a process of chemical "weaving"? (See figure 1, i).

DR. BOYER: I know of no data where K ion binding by cephalin competes with Na+. K binding by cephalin needs more study because of the role of some of the lipids in nerve tissue.

Antagonistic Effects of Sodium and Potassium on Carbohydrate Metabolism and Blood Pressure in Diabetic Children

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Our attention was first directed to the subject of the present discussion by the occurrence of freakish variations in the degree of glycosuria shown by a 15-year-old diabetic boy who manifested an inordinate craving for salt following recovery from a moderate attack of acidosis.[1] Full satisfaction of this unnatural craving, when evaluated, was found to require between 60 and 93 g. of NaCl daily with the patient on an ordinary mixed diabetic diet.

In preliminary tests on the clinical and metabolic effects of varying the salt content without altering the low Na, low K basic diet or the insulin dosage, it was found that, whenever the patient's Na intake was restricted to the 1.57 g. contained in the basic diet, glycosuria was greatly increased: whereas resumption of the high intake resulted in a marked decrease in the amounts of glucose excreted. Another and quite unexpected effect of the excessive intake of NaCl was a marked elevation of both systolic and diastolic blood pressures within 2 days after the change of regimen was instituted. With return to the very low NaCl intake, however, the temporary hypertension disappeared completely within 36 hours. Typical data are reproduced in the accompanying table.

striking on the basis of weight, presumably because of their lower Na content. The favorable effects of Na on carbohydrate metabolism in normal animals have been reported by a number of other investigators quoted elsewhere.[3]

In one control study carried out to ascertain the effect of the high-Na, low-K regimen on an essentially normal 14-year-old boy, no increase in blood pressure was induced by ingestion of 60 g. of NaCl per day, for 5 days, while the subject was maintained on the ordinary hospital diet. However, when a very low-K, basic diet was substituted for the latter, the blood pressure rose from mean values of 115 systolic and 70 diastolic to 150 systolic and 105 diastolic.

When the above tests on diabetics were repeated with K substituted for Na in approximately one-third chemically equivalent amounts, this base was found to have effects diametrically opposite to those of the high-Na regimen. Such antagonistic effects of K followed whether it was given alone with the basic, low-Na diet or simultaneously with the excessive load of Na. In both instances blood pressure was reduced from existing levels and glycosuria was increased. A hyperglycemic glycogenolytic effect of

TABLE I

THE EFFECTS OF INGESTING 64 G. OF NaCl DAILY ON A 15-YEAR-OLD BOY

Severe diabetic diet contained protein 64, fat 132 and carbohydrate 168 g. Insulin 32 units daily. No ketosis.

	Intake (grams)				*Output (grams)*						
Day	*Na*	*Cl*	*K*	*N*	*Na*	*Cl*	*K*	*N*	*Glucose*	*Weight (kilograms)*	*Blood Pressure*
1	1.57	2.43	1.48	10.36	1.86	2.27	0.86	12.40	73	38.3	116/80
2	25.16	38.84	1.48	10.36	14.26	13.38	0.86	11.10	33	38.2	116/76
3	25.16	38.84	1.48	10.36	24.17	42.28	0.86	7.87	13	40.8	140/88
4	25.16	38.84	1.48	10.36	23.55	38.16	1.40	9.23	14	40.3	150/98
5	25.16	38.84	1.48	10.36	26.56	43.06	0.93	9.63	33	40.3	174/110
6	25.16	38.84	1.48	10.36	24.38	33.58	1.56	9.67	31	40.2	166/108
7	25.16	38.84	1.48	10.36	24.83	40.36	1.40	9.78	26	40.4	164/112
8	25.16	38.84	1.48	10.36	27.28	41.85	1.21	10.87	26	40.4	176/118
9	1.57	2.43	1.48	10.36	4.99	7.88	1.44	8.78	30	40.4	164/98
10	1.57	2.43	1.48	10.36	1.86	2.41	0.82	8.91	49	39.2	130/88
11	1.57	2.43	1.48	10.36	2.57	3.80	1.13	9.47	57	39.1	112/80
12	1.57	2.43	1.48	10.36	1.75	2.24	1.05	10.87	72	38.7	106/74

Further tests with other juvenile diabetics revealed that the foregoing responses to excessive NaCl ingestion were not peculiar to this diabetic subject who manifested the inordinate craving for salt. Others without such craving responded in a similar manner, though less strikingly. The quantities of Na salt which they ingested voluntarily were smaller. The effects of Na salt, other than the Cl, such as the lactate, citrate and bicarbonate, were found to be similar to those of the Cl, but were less

K administered by vein has since been demonstrated in rats by Silvette and Britton.[4]

In contrast to the effects cited, a high-Na intake was found to have no effect on the level of glycosuria induced experimentally in dogs by phlorhizin poisoning[2] and little effect on the glycosuria and arterial hypertension of Cushing's syndrome in a preliminary study on one case tested. In a case similar to the latter, KCl in comparatively small doses temporarily corrected the hypokalemia, hypochloremia and alka-

losis manifested by the patient, but failed to affect the accompanying hypertension or glycosuria measurably during a short period of observation.

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DISCUSSION

DR. ULSTROM: During the past year we have made similar observations on several young patients with diabetes, none of which had salt craving. Our observations have been in the main similar to what McQuarrie, Thompson and Anderson previously found. However, we have had some variations that might be of interest to discuss here. The first patient studied was a young woman (a pediatric intern) with diabetes of long standing who appeared to be in good general health otherwise. She had had acute glomerulonephritis 2 years previously with mild hypertension, but following recovery she had had normal blood pressure.

The experimental conditions were similar to those described by Dr. Thompson except for the fact that the Na and K in our basic ration were actually lower, namely 0.75 g. K and 0.20 g. Na per day. After 4 days on the basic diet she was given 40 g. NaCl daily in 4 equal doses. Within 24 hours of the beginning of this high-salt regimen, the blood pressure levels rose from her normal values of 115 mm. Hg systolic and 80 diastolic to 150/100. She also developed a mild edema during this time. The glycosuria, as in the cases reported by Dr. Thompson, decreased remarkedly. She had been given 70 units of insulin daily, in divided doses during the preliminary low-salt period. This allowed each 6-hour urine specimen to contain a moderate amount of sugar. Within 36 hours after she began to ingest the extra NaCl, the urine became sugar free and it became necessary to reduce her insulin by successive steps to 50 units daily to prevent clinical hypoglycemia, the diet remaining unchanged. When the NaCl was then increased to 60 g. a day for 2 days, the effects were more marked than they had been on 40 g. a day, but diarrhea necessitated termination of the study before the effect of K could be determined. Within 36 hours after the NaCl was discontinued, the body weight and blood pressure fell to normal, and the glycosuria returned to the previous high level.

The second subject studied was a 15-year-old girl who had uncomplicated mild diabetes. After her initial period on the low Na, low K diet, she was given 40 g. of NaCl a day. The magnitude of the change in blood pressure was similar to that noted in the first patient, but the effect on carbohydrate metabolism was somewhat erratic. Glycosuria gradually increased while the fasting blood glucose, which had been running at levels around 230 mg. per cent, began to fall. When the dosage of NaCl reached 60 g. a day, the fasting blood sugar fell to 105 mg. per cent without change in the insulin dosage. The 17-ketosteroid excretion rose during the high Na period from 2 to 8 mg. per day, an effect not studied in other patients.

The final patient was a 13-year-old boy with moderately severe diabetes and mild arterial hypertension associated with chronic glomerulonephritis (see figure 1). At the beginning of the study he was quite asymptomatic and appeared to be in good general health. He showed mild albuminuria at times and the non-protein nitrogen was 52 mg. per cent at the time of his study. The serum electrolytes were normal at the beginning of the study. He received 19.8 mEq. (0.77 g.) of K and 12.5 mEq. (0.28 g.) of Na per day in the basic diet. The Na intake was increased from 12 mEq. in the preperiod to 680 mEq. a day by the addition of 40 g. NaCl per day to the regimen. There was a dramatic change in the boy. His blood pressure rose very quickly from between 128 and 148 mm. Hg systolic and between 80 and 90 diastolic to 208 systolic and 120 diastolic and his body weight increased by about 10 per cent in this short period. The NaCl was promptly discontinued after slightly more than 24 hours for fear of a more serious reaction. Unlike the response of the previously observed subjects to withdrawal of the excessive load of NaCl his blood pressure remained high and the edema persisted. The only serum electrolyte change found at the end of the short NaCl period was an increase of Cl to 113 mEq./liter from a pre-test level of 100. The edema and marked hypertension persisted for 5 days after discontinuance of the high NaCl intake when it was found that the serum K had fallen to 3.3 mEq. per liter. We then cautiously added 4 g. of KCl daily to his basic diet at this point. The blood pressure began to fall shortly thereafter. The child was in only slightly negative Na balance during this second period of low Na intake. We were amazed to see that, during the first few days of K administration, the urinary Na increased from 30 to 90 mEq. per day. He gradually lost his edema and his blood pressure returned to normal. Although we noted little change from the preliminary period until the beginning of KCl administration, the fasting blood sugar and glycosuria increased markedly at the time of KCl administration. This is consistent with the earlier findings just reported.

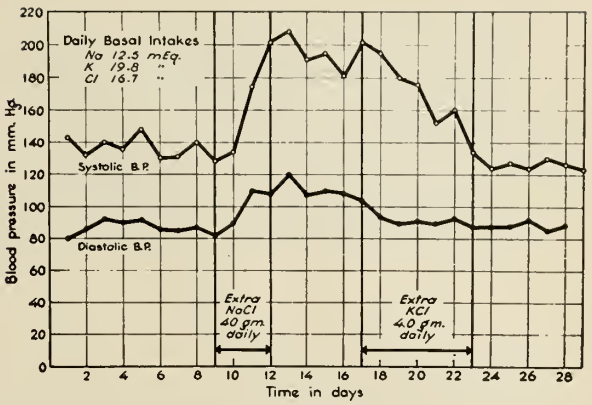

Fig. 1. Case of moderately severe diabetes and mild hypertension associated with chronic glomerulonephritis.

DR. MC QUARRIE: Our chairman, Dr. Anderson, was a member of the original team who worked on this problem and so should discuss the paper himself. There is one other observation, a corollary to what Dr. Thompson has brought out, that I should like to mention because it emphasizes the antagonism between effects of Na and K under certain conditions. An adult male on the medical service of our hospital, who suffered from extremely severe spontaneous hypoglycemia of undetermined cause was studied in respect to his responses to extreme variations in Na and K intake.

We observed a steady, though temporary, rise in his fasting blood sugar when he was induced to ingest KCl

in excessively large doses while taking the low-Na basic diet. The fasting blood glucose concentration rose from a low of 12 to a high of 93 mg. per 100 ml within 3 days with the daily dosage of KCl ranging upward from 24 to 48 grams. The transient relief from hypoglycemic symptoms was striking, but of course such radical and potentially dangerous therapy could not be long continued. Gastric irritation was naturally unbearable for more than a day or two.

DR. GUEST: I should like to ask if studies were made of renal clearance in these different periods to determine whether there were disturbances of renal function.

DR. THOMPSON: There were no renal clearances being done at the time of those particular experiments. The change in Na concentration of the serum before and during the administration of as much as 60 g. of NaCl daily was very little. There was initial retention of approximately 25 g. NaCl in the body but water was retained with it in amounts sufficient to prevent excessive concentration of Na or Cl in the extracellular fluid.

The following illustrations appeared through the courtesy of other publications: Page 163, Fig. 1: Fenn, Wallace O. and Doris M. Cobb: J. GEN. PHYSIOL., 17: (No. 5), 629-656, 1934. Page 175, Fig. 1: Cannon, Paul R., Laurence E. Frazier and Randolph H. Hughes, "Sodium as a Toxic Ion in Potassium Deficiency." METABOLISM: now in press. Page 175, Fig. 2: "NUTRITION IN THE PRACTICE OF MEDICINE," NUTRITION SYMPOSIUM, Series No. 4, 119, 1952. The National Vitamin Foundation, Inc., New York City. Page 189, Fig. 1: Guest, G. M., B. Mackler and H. C. Knowles, "Effects of Acidosis on Insulin Action and on Carbohydrate and Mineral Metabolism." DIABETES: 1:276 (No. 4), 1952. Page 190, Fig. 1, Fig. 2: Gardner, L. I., N. B. Talbot, C. D. Cook, H. Berman and Uribe Concepcion, "The Effect of Potassium Deficiency on Carbohydrate Metabolism." J. LAB. AND CLIN. MED.: 35:592, 1950. Page 191, Fig. 3: IBID. and also ENDOCRINOLOGY: 37:341, 1945. Page 194, Fig. 2: Guest, G. M. and S. Rapoport. PROC. AMER. DIABETES ASSOC.: 7:97, 1947. Page 195, Fig. 3: IBID.

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.*

Clinicopathological Conference

Minneapolis Veterans Hospital*

Edited by James F. Hammarsten, M.D.
Assisted by Robert I. Lubin, M.D. and
Donald Fry, M.D.

A 38-year-old electrician was admitted on September 1, 1950, because of back pain. He first noted low back pain early in July 1950. The pain was constant, sharp, and accentuated by motion. A few days later he developed a similar pain in the right hip. Occasionally pain would radiate down the posterior aspect of the right thigh to the popliteal space. This pain would persist for several hours and was associated with tingling in the same area. He also noted intermittent tingling and hyperesthesia on the medial portion of the right buttock. The back and hip pain were aggravated by straining associated with defecation and by coughing. Standing for long periods made the pain worse.

Shortly after the onset of his illness he began to have fever each afternoon as high as 100 to 101° F. He also developed a cough productive of one tablespoonful of thick white sputum daily. Three weeks before admission he noted dull pain over the anterior ileac crest. He had anorexia and lost 17 pounds.

He was examined by his private physician on July 24, 1950. A urinalysis disclosed 1 plus albumin and 40 to 50 red cells with 8 to 10 white cells per high-power field. The erythrocyte sedimentation rate was 108 mm. in one hour. X-ray films of the chest and spine were normal. An intravenous pyelogram was normal. X-ray films of the right hip showed "bone cysts." Cystoscopy was said to show "chronic posterior urethritis." He was treated with numerous antibiotics with no relief.

Systemic review and family history were noncontributory.

Physical examination disclosed a thin pale man who appeared chronically ill. There was moderate tenderness and spasm in the right lower quadrant of the abdomen. The right testis was absent. The prostate was slightly enlarged and a portion of the right lobe felt firm but not stoney hard. There was tenderness lateral and superior to the prostate on the right. A few small, soft lymph nodes were found in the anterior cervical region and the left axilla. The fifth lumbar vertebra and upper sacrum were tender. There was straightening of the lumbar curve. The right knee jerk was decreased and the right ankle jerk was absent. There was hypesthesia and hypalgesia on the medial portion of the right buttock and also on the anterior and lateral aspect of the right thigh.

The temperature was 98.4° F., the pulse rate 96 per minute, and the blood pressure 126 mm. Hg systolic and 80 diastolic.

The hemoglobin was 11.2 gm. per 100 ml., hematocrit 35 per cent, red blood cell count 4.08 million, MCD 7.5 microns, MCV 86 microns^3, MCH 27 micromicrons, and MCC 32 per cent. The white blood cell count varied from 12,800 to 15,700 per mm.^{3} with a differential count of 75 per cent neutrophils, 17 per cent lymphocytes, 2 per cent monocytes, 5 per cent eosinophils and 1 per cent basophils. The per cent eosinophils varied from 3 to 7. The platelets numbered 406,000 per mm.^{3} A reticulocyte count was 2 per cent. The erythrocyte sedimentation rate was 88 mm. in one hour. A blood Kahn was negative. Three urinalyses were negative and three contained a trace of albumin and an occasional erythrocyte per highpower field. Bence-Jones protein and melanin could not be demonstrated in the urine. A Coombs test was negative.

The serum protein was 6.9 gm. per 100 ml. with 4.4 gm. albumin and 2.5 globulin. The serum calcium was 9.7 mg. per 100 ml. and phosphorus 5.2 mg. per 100 ml. The blood urea nitrogen was 11.5 mg. per 100 ml. The stools were negative for occult blood, ova, and parasites. A lumbar puncture showed normal dynamics and normal spinal fluid. The fluid was examined for tumor cells and none were found. Urine cultures, including cultures for acid-fast bacilli, were negative.

The bromsulfalein retention was 16.5 per cent in 45 minutes, cephalin flocculation 0 in 48 hours, thymol turbidity 1.2 units, and serum bilirubin 0.1 mg. in 1 minute and 0.3 mg. per 100 ml. total. The prothrombin time was 20.2 seconds with the control 14.5 seconds. The alkaline phosphatase was 9.0 King-Armstrong units and the acid phosphatase

(Continued on page 206)

*Published with approval of Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Practical Clinical Chemistry, by ALMA HILLER, Ph.D., associate attending biochemist in charge of clinical chemistry, Presbyterian Hospital of the City of Chicago; associate professor of biological chemistry, University of Illinois College of Medicine, Chicago, Illinois. 1953. 266 pages. Springfield, Illinois: Charles C Thomas. $6.50.

This book, as a practical guide for technicians in clinical chemistry, fills, in a very adequate manner, a decided gap in the previously available literature. Books of a comparable nature which have been heretofore at hand either include chemistry as but one section among a number of clinical laboratory subjects, and therefore tend to be superficial, or treat chemistry in such a comprehensive fashion that the technician may become lost in the wealth of information. Neither gives the detailed information which is so valuable to the clinical chemist and which is included in Dr. Hiller's book.

The first three chapters are concerned with general laboratory techniques, and establish the standards which are necessary for the performance of reliable work. There follow twenty-five chapters, each covering the method of determination of a commonly requested constituent. For each procedure there is described in explicit detail the required special apparatus and reagents, followed by a detailed account of the procedure to be followed, including the treatment of standards. Finally, the method of calculation is given, and also the normal values obtained with the method. At the end of each chapter is given in outline form, for the convenience of the technician, the procedure previously outlined in detail.

Dr. Hiller does not give alternate methods for determination of any one constituent, and has selected those which she has found to be satisfactory. With one or two exceptions, this reviewer agrees with her choice. The value of the book would perhaps have been enhanced by the inclusion in each chapter of a short statement on the principle involved in the method. From the practical standpoint, however, this book is of great value, and the work of any clinical chemistry laboratory based on it should attain a high degree of reliability. E.F.

A Vitamin Digest, by GUY W. CLARK. 1953. 245 pages. Springfield, Illinois: Charles C Thomas. $6.50.

The stated intention of the author is to provide the basis for a good general understanding of the vitamins. In the resulting monograph the author has accomplished this purpose by presenting the facts in readable fashion and the publishers have assembled the material in an attractive manner in book form which is not in the least disjointed, as the word "digest" sometimes indicates.

Although not intended to be a complete presentation of all of the literature about the vitamins, there are numerous references grouped at the end of each chapter. The book, therefore, should be of value both as a teaching guide and a reference work. The inclusion of structural formulae also enhances its usefulness as a source of information. The brief summary of the entire book is perhaps unnecessary in a volume of this nature. R.L.T.

A Textbook of Pharmacology, by W. T. SALTER, M.D. 1952. 1240 pages. Philadelphia: W. B. Saunders Company. $15.00.

This comprehensive volume is intended for students and for up-to-date practitioners of medicine. The material is presented in a pleasant and readable fashion. The book reflects the author's intimate knowledge of the problems that confront the practicing physician.

The scope of modern pharmacology is very great and must of necessity embrace many aspects of physiology and internal medicine. This is a comprehensive textbook and the author includes much that one would ordinarily expect to find only in a volume devoted to internal medicine. It is an enormous task for a single author to discuss authoritatively such a wide range of subject matter. Having accepted such a challenge, the author must accept criticism if he exhibits any uncertainty of knowledge even in specialized fields. There are some errors discernable in this text; errors in a textbook are not excusable for they remain too long with us.

The material is presented under four headings. The first, General Principles of Pharmacology, is concise and informative. Section two, Drug Action on Physiological Mechanisms, is extensive; both fundamental and clinical aspects of pharmacology are considered. Parts three and four include Application of Drugs in Clinical Medicine and Toxicology.

There is a real need for an up-to-date textbook in the field of Pharmacology; this volume fulfills that need and can accordingly be recommended to students and physicians. F.W.H.

Mid-Century Psychiatry: edited by ROY R. GRINKER, M.D., with 13 contributors. 1953. 195 pages. Springfield, Illinois: Charles C Thomas.

This book is essentially a report of a dedication symposium June 1, 1951 for the Institute for Psychosomatic and Psychiatric Research and Training at Michael Reese Hospital. The introductory chapter briefs the history and growth of this mental hygiene effort from 1920 to the present 80-bed center and associated facilities. Its clinical history is essentially a history of clinical trends all of us have witnessed. Classical team work of psychiatrist, psychologist, and social worker began there in 1925 while Dr. David Levy was heading the group. These introductory words really set the structure and orientation for this symposium of disciplines related to human behavior. Dr. Grinker's stated aim of attempting to gain a unified theory through integrating data and communication of the disciplines sets the stage.

Contributions of the various authors are beautifully but briefly presented. They range from Percival Bailey's presentation of the cortex-mind problem and that of Ralph Gerard's neurophysiology in relation to behavior to M. Ralph Kaufmann's and Thomas W. French's review of psychoanalytic concepts favoring extended knowledge and structural concepts no longer productive.

The compiled brief synopses by chapters truly illustrate our vast increase of perspective and extension of vision in related fields, but more truly they indicate how far we are from a unified theory and from psychiatry as a unified discipline. It is a symposium well reported. R.G.H.

American College Health Association News . . .

The monthly report of Sanford E. Ayers, M.D., director of Student Health at the University of Florida, states that disease incidence of students for the month of February was normal for the period in comparison with the large influx of patients in January due to the influenza epidemic.

The average number of treatments per day during February, including Sundays and holidays, was 163. Comparative statistics are:

	February 1952	February 1953
Inpatients admitted	144	182
Total hospital days	305	422
Clinic treatments	3,207	4,152

Miss Eunice Spires, R.N., was welcomed as a new member of the nursing staff, replacing Miss Shirley MacKenzie, who resigned.

* * *

Beth Lewis, R.N., Counselor and Director of Health Services, is to be congratulated on the progress made in her two years at George Peabody College for Teachers at Nashville. Among her accomplishments are: the acceptance of the health service by the administration, the faculty, and the students; the compilation of the first annual report of the health service; the development of an accurate reporting system; the reactivation of the health committee; and the introduction of an integrated course in Personal and Community Health. Since attending the annual meeting in Boston last year, Miss Lewis has realized the importance of accurate data, of providing statistical information about the health service to the administration, and of the team approach to planning an effective college health program.

* * *

Charles Hutchinson, M.D., has been appointed Director of Student Health Service at Brown University, Rhode Island, as of July 1953.

* * *

Josephine H. Norton, M.D., Assistant University Physician at New York University, was appointed by President Max Durfee to represent the Association at the annual meeting of the National Conference for Cooperation in Health Education. Approximately forty of the sixty-two member agencies were represented at the Washington, D.C., March meeting.

The main theme running through the discussion was the cooperation of the special agencies both private and governmental with educators in general. This was coupled with a marked trend toward honest evaluation of programs and goals achieved in Health Education. Many of the agencies professed their desire to be at the disposal of institutions of higher learning throughout the country by the loan or gift of their materials such as films, film strips, slides and publications and by sending their specialists as consultants in health education, as lecturers, or in planning health projects in college health work. A recent project subsidized and staffed by the National Society for the Prevention of Blindness consisted of a survey and analysis of the health services of sixty institutions of higher learning throughout the country. Another, a bulletin published in 1948, entitled "Teacher Education for the Improvement of School Health Programs," reports two demonstration workshops co-sponsored by the National Tuberculosis Association and the Office of Education.

The announcement of the projected 4th National Conference on Health in Colleges to be held in New York in 1954 stimulated a great deal of interest and discussion. Many of the delegates expressed again the desire to cooperate in this conference. Exhibits of the American Heart Association, the National Foundation for Infantile Paralysis, the National Tuberculosis Association, the American Cancer Society, the National Society for the Prevention of Blindness and the School Health Bureau of the Metropolitan Life Insurance Company to name only a few, demonstrated that they would be well able to make an interesting contribution to the conference.

The participants expressed their desire to know more about the work of the American College Health Association, its aims and its programs, and were greatly interested in the meetings held last May in Boston.

CHILDREN AND ACCIDENTS

"Accidents are the number one crippler of children under 5 years old in the United States today," according to Lawrence J. Linck, executive director of the National Society for Crippled Children and Adults. "Every year they permanently cripple 48,000 children and necessitate medical attention for another 1½ million. Accidents in the home are preventable and it is parents who must prevent them.

Burns, falls, gunshot wounds, poisoning, and severe cuts are all accidents which happen most frequently at home and are childhood's great killers and disablers, Mr. Linck stated. He said that one out of five deaths due to burns is a child under five and that victims of fatal poisoning accidents are most often children not yet five years old. He underscored the fact that these accidents most commonly occur at home, where children should be the safest.

"Worst of all, the accident toll is steadily climbing and our problem is becoming steadily more critical," the executive director pointed out. "It is appalling that 1,900 children under 15 died of burns during the last year and of that number two-thirds were supposedly carefully protected youngsters under five. Five hundred children under 15 died in falls, three out of five being children under 5 years old who fell downstairs, off porch railings, or out of windows in their homes. Children under five were also the chief victims of poisoning which killed a total of 500 youngsters under 15."

News Briefs . . .

Reports on Progress in Pediatrics . . .

IRVINE MCQUARRIE

DR. IRVINE MCQUARRIE of the University of Minnesota Medical School reported on progress in pediatrics at the First Western Hemisphere Conference of the World Medical Association held April 21-25 in Richmond, Virginia. All nineteen areas of specialization as defined by the Advisory Board for Medical Specialties were represented at the conference and spokesmen listed the outstanding accomplishments in each field.

Advances in pediatrics listed by Dr. McQuarrie were the discovery of the relationship between contamination of water and food supplies and enteric or diarrheal diseases in infants and young children as the most spectacular from the standpoint of reducing infant mortality. He also cited the development of artificial feeding of infants, vaccination and heart surgery as among the most significant improvements in the care of children.

Other major advances from the viewpont of specialists included the development of asepsis in surgery, knowledge of hormones of glands of internal secretion, and the introduction of psychoanalytic techniques into psychiatry.

Delegates from Upper Midwest to World Medical Conference

GUESTS OF HONOR at the recent World Medical Conference in Richmond, Va., included the following physicians and their wives. These senior physicians were chosen by the governors of their respective states — one from each state — to attend the meeting.

Doctors from the Upper Midwest who acted as official state representatives were: Frederick O. Gronvold, Fargo, NORTH DAKOTA; T. J. Billion, Sioux Falls, SOUTH DAKOTA; Rudolph A. Beise, Brainerd, MINNESOTA; George B. Crow, Burlington, IOWA; W. B. Campbell, Waukesha, WISCONSIN, and B. K. Kilbourne, Hardin, MONTANA.

A grant by the A. H. Robins Co. Inc., pharmaceutical house of Richmond, made the conference possible. The company is observing its 75th anniversary this year. In reviewing the total picture of medical progress, most of the honor guests and speakers believed that science can and will find the answers to current medical problems, and, in the process, make life better as well as longer in the years to come. Past advances seemed to indicate, however, that man really knows truly little about his own personal life processes.

GEORGE B. CROW
IOWA

B. K. KILBOURNE
MONTANA

T. J. BILLION
SOUTH DAKOTA

FREDERICK O. GRONVOLD
NORTH DAKOTA

RUDOLPH A. BEISE
MINNSOTA

W. B. CAMPBELL
WISCONSIN

CLINICOPATHOLOGICAL CONFERENCE

(Continued from page 201)

1.8. The fecal urobilinogen was 73.5 mg. in 24 hours.

Two tests for urinary prolans were negative. A bone marrow was normal except for a slight increase in plasma cells. Bronchoscopy, proctoscopy, and an electrocardiogram were normal. Cystoscopy was normal except that the lateral lobes of the prostate appeared hyperemic. A tuberculin skin test was positive.

X-ray films of the chest, skull, lumbar and sacral spine and right hip were negative. X-ray studies after a barium meal and enema were negative. Intravenous and retrograde pyelograms were normal. An x-ray film of the pelvis showed extensive mottling of the right ileum (figure 1).

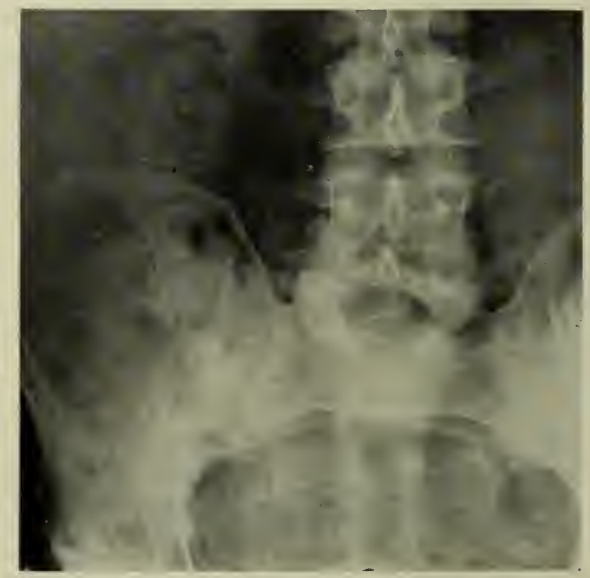

Fig. 1. X-ray film of the pelvis showing mottling of the right ileum.

He continued to have pain which required narcotics for relief. His temperature rose to about 101° F. each afternoon. He developed tenderness over the right ileac crest. During the third week in the hospital, after giving 1/12 grain morphine, one examiner felt a mass in the right lower quadrant of the abdomen and another mass superior to the prostate on the right. The patient continued to lose weight.

After several transfusions an operation was performed on October 17, 1950.

DISCUSSION

DR. HOWARD HORNS*: In reviewing this case the first item of note is that the presenting complaint is low back pain which has been present three or four months. Without going through the vast number of situations which produce back pain, I think

*Associate Professor nf Medicine and Assistant Dean, Medical Schnol, University of Minnesota, Minneapolis, Minnesota. On military leave.

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we can narrow it down by attention to some of the other findings. The pain radiated down the posterior aspect of the thigh and was associated with tingling which suggests peripheral nerve or rootlet involvement. The right patellar reflex is diminished, the ankle jerk absent, and there is hypesthesia and hypalgesia over the anterior and lateral aspect of the right thigh. All of these findings suggest involvement of the second, third, and possibly fourth lumbar segments. The radiation of pain to the posterior aspect of the thigh suggests sacral involvement which might indicate an extensive affair and argue against a prolapsed intervertebral disc.

The patient is febrile. This suggests either an inflammatory or a malignant lesion. The elevated white blood cell count is consistent with a malignancy. The x-ray evidence would favor a malignancy. The real question is: What is the primary site?

The bone lesions I assume are metastases. The fever and red cells in the urine suggest a hypernephroma. The febrile course particularly suggests that. However, the pyelograms are negative. Several other possible primary sites are reasonably excluded by the x-ray evidence.

The man had an undescended testis which strongly suggests an additional site for the primary lesion. Undescended testes have a much higher incidence of malignancy than do testes in the scrotum. The ratio is about 20 to 1. The tumors of the testes are of several types. The most common one is a seminoma. There are several things about this case which are not entirely typical of a tumor of the testes. The location of the metastases, particularly, is atypical. The route of metastases is by way of the lymphatics to the periaortic nodes and then to the lungs. Metastases to the bone are usually late. The test for urinary prolans does not help much since it would only be elevated were the tumor a chorionepithelioma.

I believe the diagnosis lies between a hypernephroma and a seminoma and will choose the latter.

DR. BELL: Would you consider the prostate as a a site for the primary?

DR. HORNS: I would think that unlikely since there is no tumor palpated in the prostate and the acid phosphatase is normal.

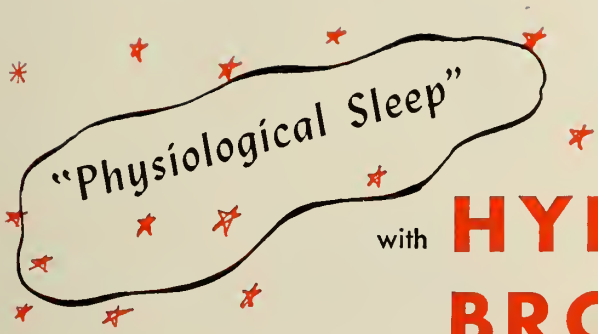
DR. HELLER: I would make a diagnosis of hypernephroma because of the hematuria and prolonged unexplained fever.

DR. HAMMARSTEN: The students submitted a variety of diagnoses: tuberculosis of the spine, Hodgkin's disease, perirenal abscess, osteomyelitis, and hypernephroma.

DIAGNOSES

Clinical diagnosis: Abdominal Hodgkin's disease.
Dr. Horn's diagnosis: 1. Seminoma or 2. Hyper-

(Continued on page 210)



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Beckman, Harvey, Treatment in General Practice, 5th ed., P. 813, W. B Saunders Co., Philadelphia (1946)

nephroma. Anatomical diagnosis: Hypernephroma, left.

PATHOLOGICAL DISCUSSION

DR. GLEASON: The operation was an exploratory laparotomy. Astonishingly the findings were on the left. In the lower pole of the kidney was a round mass 6 cm. in diameter. There were nodes at the hilum of the kidney. The kidney was removed. He was treated with x-ray, developed a severe anemia, and was given blood transfusions. He died on February 4, 1951.

At autopsy we were unable to find a right testis. There was tumor on the peritoneum, in the liver, lungs, and lymph nodes. There was a 5 mm. tumor nodule in the right kidney. The tumor on all sections was similar and was a hypernephroma.

A RESIDENT: How often does a hypernephroma metastasize to the other kidney?

DR. BELL: Autopsy statistics indicate in about 10 per cent.

DR. HORNS: I would like to point out one peculiarity of hypernephromas. As far as I know it is the only tumor that metastasizes to the bronchial mucosa.

News Briefs . . .

PUBLIC SERVICE ADVERTISING

A new series of education advertisements stressing the theme "In the hands of your physician, you're in good hands," has been announced by Parke Davis, pharmaceutical firm, for release in a wide range of national magazines. Believing that there is a present-day trend to tear-down public confidence in the practicing physician and a growing tendency among patients to dictate treatment and medication, the company will offer these informative messages as a public service to physicians. Aimed at the general reading public, the ads will run in the Saturday Evening Post, Life, Woman's Home Companion, Time, Collier's, Good Housekeeping, This Week, and Today's Health. This advertising campaign represents the company's twenty-fifth year of "See Your Doctor" advertisements.

FINANCIAL HELP FOR MEDICAL SCHOOLS

Steps to mobilize private financial support in behalf of the nation's 79 medical schools were discussed recently at a meeting of industrialists, business leaders and educators in Philadelphia. This meeting was sponsored by Smith, Kline & French Laboratories. Under the Committee of American Industry of the National Fund for Medical Education, a nationwide solicitation campaign will be conducted to help overcome financial deficits facing many medical schools.

(Continued on page 212)

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NEW BRIEFS

(Continued from 210)

DO YOU KNOW ABOUT

A valuable tool in the public relations work of state and county medical societies is the *"Your Doctor"* film. Many local societies encourage commercial theaters to book the film through RKO-Radio Pictures and by arranging showings throughout the community. The 16 mm. version is available on loan from Modern Talking Picture Service, Inc., 45 Rockefeller Plaza, New York 20, New York. The only charge is for postage and insurance. Individual prints may be purchased at $70 per copy from RKO-Radio Pictures, and requests will be filled by society offices.

Current statistics on medical education in the United States have been compiled by the American Medical Association in a pocket-size booklet entitled, *"Factbook on Medical Education."* Written in a question-and-answer style the booklet contains data on enrollments, financial support, faculty, and new medical schools. The booklet will be distributed to state and county medical society officers, A.M.A. delegates and officers, newspaper and magazine writers, and allied health organizations. Additional copies will be available for distribution by state and county medical societies.

SCHERING AWARD WINNERS ANNOUNCED

The three winners of the 1952 seventh annual Schering Award competition among medical students: Edward Allen Jones, a sophomore at Meharry Medical College, Nashville, Tennessee, native of Atlanta, for the outstanding paper on "Steroid Hormones in Geriatrics."

The award for the outstanding paper on "The Topical Uses of Antihistamines" was given to Seymour Cohen, Watertown, New York, senior medical student at the State University of New York at Syracuse.

The third $500 award went to William Howard Spencer, born in New York City, junior at the School of Medicine, University of California Medical Center, San Francisco. His paper on "Chemotherapy of the Eye" was selected as the most meritorious.

The Schering Award seeks to encourage among the nation's medical students original reporting and exploration of recent developments in therapy, in the hope that they will later contribute to the general knowledge throughout the medical profession.

The Schering Corporation of Bloomfield, New Jersey, sponsor of the award, is the world's largest producer of sex hormones. Instrumental in advancing clinical research in endocrinology, the company has developed potent hormone preparations.

WANTED: BLOOD

The Office of Defense Mobilization is urging civilians to respond to the call for blood donations. To meet the present-day need for whole blood and derivatives, the National Blood program must receive the voluntary donation of over 5,000,000 pints this year. Blood is vital to federal defense for building reserves of serum albumin, to accident victims in need of whole blood transfusions, to wounded service men in need of shock units of serum albumin, and to children exposed to polio who need blood derivative gamma globulin.

NEW REPORT IN POLIO RESEARCH

A research finding that should have immediate effects in assisting diagnostic laboratories, including many State Health Departments, to a cheaper and quicker method of diagnosing poliomyelitis cases was announced recently by the Public Health Service of the U. S. Department of Health, Education, and Welfare.

The finding is the adaptation to growth in experimental mice of the third of the three known strains of polio virus, the type believed to be the cause of most of the cases of human polio.

The discovery was the work of Dr. C. P. Li and Dr. Morris Schaeffer, both of the Virus and Rickettsia Laboratory in Montgomery, Alabama, which is part of the Public Health Service's Communicable Disease Center. The complete report of their work is published in the current issue of the *Proceedings of the Society for Experimental Biology and Medicine.*

With the completion of this phase of the research, all three of the polio virus strains have been adapted to mice by Public Health Service scientists, either at the National Institutes of Health, in Bethesda, Maryland, or in the Montgomery laboratory. Researchers in the polio field have been working especially hard to propagate this only remaining unadapted strain in mice since the second strain was adapted in 1951, and with other recent advances in polio research this finding will assist materially in conquering the disease.

The discovery has several specific results. It makes possible demonstration of the serum antibody response in a polio case through a relatively simple mouse test, and it will permit a more available accurate diagnosis of polio specimens by materially reducing the cost of antibody studies.

It will also reduce the cost of epidemic studies, making possible a better understanding of the mode of spread of the disease and how it can be prevented, through surveys for the presence of antibodies. And finally, it contributes a valuable new tool for the assessment of gamma globulin and vaccination methods soon to be weighed for their value in the prevention and control of polio.

In effect, the finding provides another simplified method that has been needed in the polio research field. Research and diagnosis have been retarded by the necessity for using monkeys and chimpanzees, much more expensive and difficult to work with than mice. This new diagnostic tool can now be added to the tissue-culture method, which has come into considerable use since its discovery in 1939.

CHANGE OF ADDRESS

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FEDERAL SECURITY AGENCY REPORTS ON DEATH RATE

As more people survive the hazards of infancy and childhood, more enter the age groups in which cancer and the cardiovascular-renal diseases take their toll. The Annual Report of the Federal Security Agency for 1952 reports that the death rate for cancer was 143 per 100,000 in 1951, and the cardiovascular-renal death rate was 512 per 100,000. The combined rate of 655 accounted for more than two-thirds of all deaths in the United States last year. In 1900 they were responsible for less than one-fourth of all deaths.

The agency says:

"Reports of notifiable diseases show similar evidence of control of environmental sanitation and prevention of communicable diseases. Diphtheria, smallpox, and typhoid fever, for which we have adequate preventive and control measures, continue to show moderate to substantial decreases in incidence. From the 1950 levels reported cases of diphtheria dropped 30 per cent; the declines were 60 per cent for smallpox, 10 per cent for typhoid fever, and 40 per cent for whooping cough.

The number of cases of poliomyelitis was 28,386 in 1951 as compared with 33,300 in 1950 and 42,033 in 1949, one of the recent years of high incidence.

The reports for 1951 show a decline in the number of cases of influenza, pneumonia, Rocky Mountain spotted fever, and tularemia. An increase in malaria can be attributed in part to infected military personnel who returned from Korea; 5,600 cases were reported in 1951 as against 2,184 in 1950.

Official reports of approximately 200 epidemics in the United States in 1951 indicated that food, including milk and milk products, was the actual or suspected source of infection in about 75 per cent of this total.

Like the communicable diseases, many of the chronic diseases can be controlled. Many can be prevented through adequate safeguards against occupational hazards. Many can be arrested if they are recognized before they have run their course or have given rise to new and secondary conditions."

The Journal Lancet

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

Hormone-Induced Hypopotassemia

*A Critical Resume**

EDMUND B. FLINK, M.D., Ph.D.†
University of Minnesota, Minneapolis

THE IMPORTANCE of function of the adrenal cortex in regulation of Na and K balance and the history of development of this subject was discussed by Loeb.[1] Patients in Addisonian crisis have a decrease in serum Na to as low as 100 mEq./l and an increase of serum K to occasionally as high as 10 mEq./l. Sodium excretion is increased but K excretion is decreased. Potassium administration is deleterious and K deprivation is beneficial in Addison's disease. Thus, K metabolism has become linked to function of the adrenal cortex because of accumulation of K in adrenal insufficiency and because of the reverse in Cushing's syndrome. That adrenal hormones could produce reduction in serum K was predicted from the recognition of hypopotassemic alkalosis in Cushing's syndrome.[2]

The pathogenesis of hormone induced hypopotassemia is straightforward. Either the hormone produces a negative K balance by causing its excretion in the urine or the hormone causes a transfer of K from serum to cells. However, the exact mechanism of action of the hormone on the kidney or on the cell membrane is not clear. Adrenal cortical hormones tend to produce a negative K balance which in turn can result in hypopotassemia. A considerable total K deficit occurs because K is lost from cells also. Testosterone and insulin on the other hand cause transfer of K from serum to cells.

In 1937, the partial synthesis of desoxycorticosterone acetate (DCA) was accomplished by Reichstin and Steiger and this hormone became available for general use in 1938. It soon proved to be of value in the treatment of adrenal insufficiency.

Desoxycorticosterone acetate causes retention of Na and excretion of K in normal and adrenalectomized animals.[3] DCA in large doses given to dogs produces a diabetes insipidus-like syndrome and muscle paralysis due to loss of K. The hypopotassemic paralysis could be prevented by giving KCl but the diabetes insipidus-like syndrome continued.[4] DCA has produced K depletion of the same magnitude in rats as in dogs, but paralysis does not occur.[5] Heart lesions which occur are identical with the changes occurring in rats fed a K deficient diet. The heart lesions and other changes can be prevented by giving KCl to these animals. Many experiments have confirmed the observation of K depletion induced by DCA. Dose and duration of administration, K intake and Na intake determine the severity of hypopotassemia produced.[6]

Clinical reports of toxicity of DCA appeared shortly after it became available for trial.[1,7,8,12] For instance Loeb[1] found that the serum K was below 4 mEq./l in 9 of 10 patients and was 2.9 and 2.4 in 2 of these. These reports dealt with hypertension, congestive heart failure, systemic or respiratory paralysis and sudden death. It soon became evident that it was unwise to combine DCA therapy and a low K diet and that it was advisable to allow moderate rather than a high Na intake.[8]

Measurements of renal effects of DCA have been made in various ways. Thorn[3] was the first to show that the total daily K excretion was increased by DCA. Sartorious and Roberts[9] measured the acute effects in normal dogs in terms of mEq. of K/min. and found a twofold increase in excretion. Another expression of the effect of DCA on renal function is the increase of the C_K/GF_K ratio by Mudge and co-workers. This ratio increased from .12 to .48 when DCA (2.24 mg./kg.) was given. The most recent expression of the action of DCA is the change in Na/K ratio in adrenalectomized rats. This is a sensitive way to assay for small quantities of DCA.[11]

*Published with approval of Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Chief, Medical Service, Veterans Administration Hospital, Minneapolis, Minnesota.

‡C_K/GF_K is the ratio of total renal clearance of potassium to that cleared by glomerular filtration.

Other adrenal steroids have electrolyte regulatory actions which are qualitatively similar to DCA but are quantitatively much less pronounced. Although the comparison of activity is not complete, Simpson and Tait's[11] data indicate the order of magnitude of the effects of these hormones on Na/K ratio in adrenalectomized rats using DCA as point of reference.

DCA	*100*
Compound A	6.7
Compound B	14.3
Compound E	5.2
Compound F	7.6
Compound S	7.9
A.C.E./ml.	150.0

Adrenal cortical extract usually is not administered in large enough doses to produce hypopotassema, but McGavack[12] reported a patient with Addison's disease maintained on large amounts of intravenous saline and glucose and cortical extract (40 ml./d). In addition this patient did not eat much. Potassium was 2.2 mEq./l, profound weakness was present and death occurred shortly afterward.

Cortisone (compound E) has been a frequent recent cause of hypopotassemia. Sprague and coworkers[13] reviewed the experiences on the physiological effects of cortisone and corticotropin (ACTH). Cortisone did not produce hypopotassemia or negative K balance at a dose level of 100 mg./d. but often did on 200 mg./d. ACTH produced hypopotassemia and negative balance at a dose level of 100 mg./d. Though variable, the experience of many investigators has indicated that hypopotassemia is related directly to the duration and dosage and Na intake and inversely to the K intake during ACTH or cortisone therapy.

Eleven dehydrocorticosterone (compound A) has not been available in large quantity, but it causes an excretion of K when administered to Addisonian patients. A dose of 30 mg./d. causes Na retention and K excretion (daily average from 53 mEq./d. to 78 mEq./d.).[14] It is fair to predict that compound A can produce hypopotassemia.

Corticosterone (compound B) has been found to be more powerful than compounds A, E, or F in electrolyte regulation.[15] It is potentially able to produce hypopotassemia.

17–hydroxycorticosterone (compound F) is capable of producing K diuresis and hence is potentially able to produce hypopotassemia. Adrenalin administered in small doses to man causes a significant but transitory decrease in serum K and a decrease in urine K excretion.[16]

Testosterone propionate and methyl testosterone have produced hypopotassemia by the transfer of K from serum into cells. There are a positive K balance and a positive N balance. There is more retention of K than of N. The lowest serum K recorded is 0.4 mEq./l observed during testosterone therapy of a dwarf.[17] Muscle paralysis and electrocardiographic changes did not occur in spite of very low serum K levels in 4 patients with various diseases. Leonard[18] has shown that testosterone causes considerable increase in muscle glycogen in castrate male rats as well as in normal rats. The storage of glycogen could account for some of the intracellular transfer of K.

Insulin induced hypopotassemia which was described first by Harrop and Benedict[19] will be discussed by Dr. Danowski.

Posterior pituitary extract causes increased K excretion when given in small doses.[9] The effect on K excretion is additive with that of DCA. Posterior pituitary extracts probably will not produce hypopotassemia. In very large doses administered to dogs it has produced hyperpotassemia.

SUMMARY

1. Some hormones are capable of producing hypopotassemia by causing a negative overall K balance. Hormones of this group include DCA, A.C.E., ACTH, compounds A, B, E and F.

2. Other hormones (insulin and testosterone) cause transfer of potassium from plasma into cells.

3. Adrenalin and pituitrin have but transitory effects.

4. In addition, multiple non-hormonal factors influence development of hypopotassemia. The most important of these is the potassium and sodium intake, assuming that there is a caloric balance.

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The discussion of this paper follows that of Dr. Sprague.

Hypopotassemia and Other Electrolyte Disturbances in Cushing's Syndrome

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SOME PATIENTS with Cushing's syndrome* exhibit, as one manifestation of adrenal cortical hyperfunction, a disturbance of the plasma electrolytes which, in its classical form, is characterized by decreased concentrations of K and Cl, increased concentration of bicarbonate and increased pH. The concentration of Na may or may not be increased. The condition has usually been designated as hypochloremic, hypopotassemic alkalosis.

HISTORICAL DATA

The first mention of alkalosis in Cushing's syndrome was by Kepler[1] in 1933. He described 4 female patients who had the clinical features described by Cushing,[2] one of whom was remarkable because of spontaneous, persistent alkalosis (plasma bicarbonate 50.5 mEq./l.) associated with a low concentration of plasma Cl and intense diabetes. At necropsy the adrenal glands were found to be enlarged, their total weight being 49 g. The second recorded instance of Cushing's syndrome associated with alkalosis was reported by Walters, Wilder and Kepler[3] one year later. Their patient was also a woman who had diabetes. The concentrations of plasma Cl and serum K were low (84.5 and 2.7 mEq./l, respectively) and the level of bicarbonate was elevated (39 mEq./l of plasma). Bilateral resection of enlarged, hyperplastic adrenal glands was followed by improvement of the electrolyte abnormalities.

The third instance of this state was reported by McQuarrie, Johnson and Ziegler[4] in 1937. Their patient was a woman with severe diabetes and severe, persistent hypochloremic alkalosis associated with hypopotassemia and elevated plasma pH. Ingestion of as much as 40 g. of NaCl daily did not materially alter the disturbance of the plasma electrolytes. In contrast, ingestion of 10 g. of KCl daily for 5 days restored the plasma K, Cl and bicarbonate to normal levels and prompted the suggestion that "the Cl concentration was in some way conditioned by the K level." Another early case was that of a man reported by Willson, Power and Kepler[5] in 1940. The patient was shown to be in negative K balance. As in the foregoing case, it was found that the disturbance of the plasma electrolytes could be corrected, though only temporarily, by administration of KCl.

Since then numerous other cases have been reported. It is now recognized that disturbances of the plasma electrolytes are not a feature of all cases of Cushing's syndrome, and that frank diabetes is not necessarily present.

INCIDENCE OF ELECTROLYTE DISTURBANCES IN CUSHING'S SYNDROME

Cushing's syndrome is associated with either hyperplasia† or tumor of the adrenal cortex. At the Mayo Clinic, among 83 patients who had Cushing's syndrome associated with hyperplasia, 34 had alkalosis of some degree (defined as plasma bicarbonate in excess of 30 mEq./l) (see table I). Only 11, however, had both hypochloremia and hypopotassemia, in addition to increased bicarbonate. The remaining patients with alkalosis exhibited various combinations of abnormalities of the plasma Na, Cl and K.

TABLE I
INCIDENCE OF ALKALOSIS IN CUSHING'S SYNDROME

		Alkalosis		*Alkalosis with low plasma K and Cl*	
	Cases	*Cases*	*Per cent*	*Cases*	*Per cent*
Adrenal cortical hyperplasia	83	34	41	11	13
Adrenal cortical tumor	17	6	35	3	18
Total	100	40	40	14	14

Every patient who had pronounced hypopotassemia also had alkalosis.

In our experience, cases of Cushing's syndrome associated with tumor of the adrenal cortex are far less numerous than those associated with hyperplasia. Among 17 such patients seen at the Mayo Clinic, 6 had alkalosis of some degree (table I). Only 3 of these had both hypochloremia and hypopotassemia.

The foregoing data do not seem to indicate a significant difference in the incidence of alkalosis in

*The term Cushing's syndrome should be reserved for patients who have most or all of the following physical features: a distinctive habitus characterized by obesity or an abnormal distribution of fat and wasting of muscles so that the face, neck and trunk appear obese and the extremities thin; muscular weakness; hypertension; osteoporosis; amenorrhea or impotence; hirsutism and acne of some degree in the absence of other evidences of virilization; thin skin with purplish striations and a tendency to ecchymosis, and a cervicothoracic fat pad. Usually the urine is alkaline, lymphopenia and eosinopenia are present, and carbohydrate tolerance is impaired.

†In what follows, the term "adrenal cortical hyperplasia" will be used in a loose physiologic sense to designate hyperfunctioning adrenal glands which are not the site of a tumor. In our experience, such adrenal glands in some patients with frank Cushing's syndrome are of normal weight and definite cytologic evidence of hyperplasia may not be demonstrated in sections stained with hematoxylin and eosin.

cases with and without tumor of the adrenal cortex. It is our impression that pronounced disturbances of the plasma electrolytes occur for the most part in patients who have other severe manifestations of Cushing's syndrome; however, exceptions to this are observed.

PATHOGENESIS OF ALKALOSIS IN CUSHING'S SYNDROME

Several lines of evidence indicate that the characteristic alkalosis of Cushing's syndrome, as well as all the other features of the condition, is a consequence of excessive secretory activity of the adrenal cortices, regardless of what lesions may be present in the anterior pituitary, including basophilic tumor and Crooke's changes. The majority of patients have either enlarged, hyperplastic adrenal glands or an adrenal cortical tumor. Studies of the urinary formaldehydogenic steroids usually reveal unequivocal evidence of adrenal cortical hyperactivity. In one case studied by Mason and Sprague,[6] the adrenal hormone 17-hydroxycorticosterone (compound F) was isolated from the urine. The alkalosis is corrected by subtotal or total adrenalectomy or by removal of a tumor of the adrenal cortex. McQuarrie, Johnson and Ziegler[4] pointed out that in many respects the abnormalities of the plasma electrolytes in their case of Cushing's syndrome were the opposite of those observed in untreated Addison's disease. Finally, with the availability of cortisone and corticotropin in amounts sufficiently large to permit administration to human subjects, it has been found that both of these substances are capable of producing virtually all of the symptoms and signs of Cushing's syndrome, including alkalosis.[7] The occurrence of the same type of alkalosis in some patients subjected to the stress of major surgical procedures may be related, in part at least, to adrenal cortical hyperfunction.[8]

On the basis of the foregoing evidence, it can be concluded that the alkalosis of Cushing's syndrome results from excessive secretion of adrenal hormones, and that the specific steroid which is probably most at fault is one closely related to cortisone, perhaps 17-hydroxycorticosterone (compound F).

Although it has not yet been established with certainty that antecedent loss of K, owing to adrenal cortical hyperfunction, is a necessary condition for the development of hypochloremia and alkalosis, there is considerable indirect evidence that this is actually the case. Potassium deficiency of some degree can be presumed to be a feature in most cases of Cushing's syndrome, whether or not alkalosis and hypopotassemia exist. Kepler and associates[9] found low concentrations of K in the muscles of 3 patients with untreated Cushing's syndrome (2 had adrenal cortical hyperplasia and 1, an adrenal cortical tumor). In 1 of the 3 the value for serum K was normal, and in 2 it was low. The studies of Willson, Power and Kepler[5] suggested that the low level of serum K in their case was based on excessive urinary excretion of K. Attempts at correction of the alkalosis by administration of Cl ion in the form of NaCl or NH_4Cl meet with only transitory success, for the administered Cl is rapidly excreted in the urine. Administration of KCl, on the other hand, as first demonstrated by McQuarrie, Johnson and Ziegler[4] results in more lasting, though still temporary, correction of the abnormalities of the plasma electrolytes. This is illustrated by data of Willson, Power and Kepler[5] (table II) and by our own data (figure 1). Willson, Power and Kepler found that administration of K citrate without additional amounts of Cl, beyond that contained in the diet, restored the concentration of serum K to normal and corrected in part the hypochloremia and alkalosis. Large amounts of K were retained. Kepler and associates[10] found that rigid restriction of the intake of K resulted in a slight intensification of alkalosis in one case.

TABLE II

PLASMA ELECTROLYTES IN A CASE OF CUSHING'S SYNDROME IN RELATION TO INTAKE OF POTASSIUM AND CHLORIDE

Intake, mEq. per day		*Days of*	*Plasma electrolytes, mEq. per liter*			
K	*Cl*	*intake*	*Na*	*K*	*Cl*	*HCO_3*
Normal dietary	Normal dietary		137.0°	2.2°	78.1°	46.0°
212.5	206.3	7	141.0	3.5	99.0	32.0
176.8	201.3	6	134.0	4.8	99.8	22.5
67.3	239.3	8	144.0	2.7	98.7	33.0

°Value obtained before start of metabolic study.
Data adapted from Willson, Power and Kepler.[5]

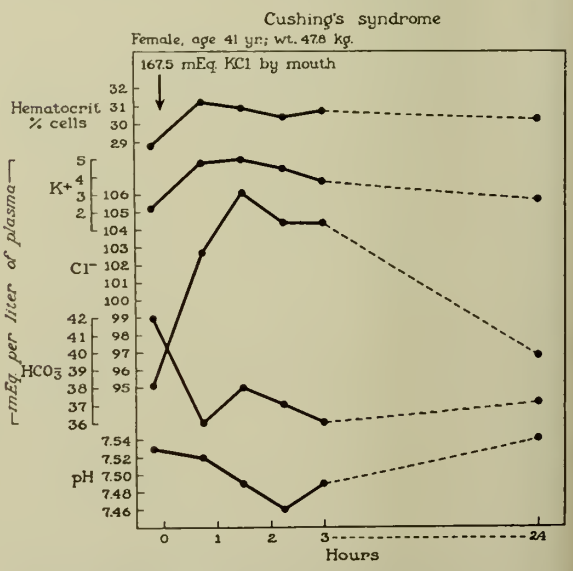

Fig. 1. Correction of hypochloremic, hypopotassemic alkalosis in a woman with Cushing's syndrome by oral administration of a single large dose of KCl.

After removal of an adrenal cortical tumor, similar restriction of K intake did not induce alkalosis (table III). In a later study of the same patient a negative K balance was corrected by administration of large amounts of KCl. Teabeaut, Engel and Taylor[11] reported the correction of hypochloremia and

TABLE III

PLASMA ELECTROLYTES IN A CASE OF CUSHING'S SYNDROME BEFORE AND AFTER REMOVAL AND AFTER RECURRENCE OF MALIGNANT ADRENAL CORTICAL TUMOR

K intake, mEq. per day	*mEq. per liter*			
	Na	*K*	*Cl*	*HCO_3*
BEFORE REMOVAL OF TUMOR				
47	140	3.9	95	34
126	138	5.7	98	29
AFTER REMOVAL OF TUMOR				
42	139	4.7	102	26
AFTER RECURRENCE OF TUMOR				
Normal diet	149	2.2	91	39

Data from Kepler, Sprague, Clagett, Power, Mason and Rogers.[10]

alkalosis, but not of hypopotassemia, in a patient with Cushing's syndrome by administration of testosterone propionate, possibly through restoration of intracellular K.

Darrow and associates[12] and others have shown that in experimental animals alkalosis, hypochloremia and hypopotassemia can be induced by various measures which lead to K deficiency. These include restriction of intake of K and administration of desoxycorticosterone acetate alone or in conjunction with a low intake of K. Similar unpublished data of Locke, Higgins and Power[13] are shown in table IV. In such animals K in the muscle becomes markedly depleted. Darrow and associates[12] have shown that depletion of K in the muscle is associated with an increase of Na in the muscle and an increase of serum bicarbonate.

There is thus much indirect evidence suggesting that K depletion plays an important, possibly primary, role in the pathogenesis of alkalosis in Cushing's syndrome.

COMMENT

The electrolyte disturbances of Cushing's syndrome, which are a consequence of the action of excessive amounts of adrenal hormones, probably cortisone-like, can be summarized as follows: Presumably in all cases there is a depletion of intracellular K and probably an increase in intracellular Na. In some, particularly those in which the disease is severe, there is, in addition, a lowering of the extracellular concentration of K, as measured in the blood plasma or serum. When hypopotassemia exists, and occasionally when it does not, there is likely to be hypochloremia and alkalosis. Indirect evidence suggests that K deficiency is a necessary condition for the development of hypochloremia and alkalosis; this, however, is not established with certainty. In addition, hypernatremia, due to the Na-retaining activity of adrenal steroids, may or may not be present. Occasionally retention of Na is sufficiently marked to cause edema.

The muscular weakness which is a characteristic feature of Cushing's syndrome is probably not solely a result of K deficiency, but rather in part a consequence of wasting of muscle due to the catabolic action of cortisone-like steroids on protein. However, extreme degrees of weakness, or even paralysis, are occasionally observed in patients with Cushing's syndrome and are dramatically improved by administration of K. In such instances K deficiency appears to be an important factor in the muscular weakness.

While administration of KCl will correct the electrolyte abnormalities of Cushing's syndrome, it is to be noted that it will not correct the other features of the syndrome.

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TABLE IV

EFFECTS OF LOW-POTASSIUM DIETS AND ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE (DCA) ON SOME CONSTITUENTS OF RAT BLOOD°

Group	*Sex*	*No. rats*	*No. samples†*	*Diet‡*	*DCA*	*Arterial blood, pH§*	*CO_2 content*	*Arterial plasma*		
								Cl	*K*	*Na*
								milliequivalents per liter§		
1	M	9	4	AK	O	7.42 ± 0.01	28.2 ± 0.6	101.8 ± 0.3	6.3 ± 0.7	137.0 ± 2.0
2	M	9	4	AK	+	7.49 ± 0.01	32.3 ± 0.5	97.1 ± 0.3	4.6 ± 0.1	139.2 ± 0.6
3	M	9	4	LK	O	7.51 ± 0.01	39.2 ± 1.3	88.3 ± 1.6	5.4 ± 0.5	136.2 ± 0.1
4	M	10	4	LK	+	7.56 ± 0.00	43.5 ± 2.9	84.1 ± 3.1	4.9 ± 0.3	133.7 ± 3.2

°Data from Locke, Higgins and Power.13 Animals on diet for 71 days. DCA administered for the last 14 days of the experiment (1 mg./100 g. body weight per day).
†A "sample" consisted of the mixed blood obtained from 2 to 3 rats.
‡AK = adequate K diet. LK = low K diet.
§Mean of the values obtained on analysis of the samples and standard error of the mean.

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DISCUSSION

DR. MC QUARRIE: They always have such an abundance of clinical material at the Mayo Clinic that, whenever we are looking for variations or special points to round out our inquries we know that our colleagues working there may have the answers. So, I would like to ask Dr. Sprague one question right off about "Cushing's disease." We do not hear much now about "'Cushing's disease" or basophilic adenoma of the pituitary. I talked with Dr. Cushing concerning his concept of the pituitary-adrenal relationship very early in the course of our own study on the electrolyte metabolism in hypercortico-adrenalism. He said that adrenals were hypertrophied in all of his cases but this was secondary to the abnormality of the activity of pituitary tumor.

I would like to ask you, Dr. Sprague, if your study of cases of that character, i. e., cases of true basophilic adenoma of the pituitary, not merely cases showing the Crooke's phenomenon which appears to occur in nearly all cases of Cushing's syndrome, if you see similar electrolyte changes. We have not had the opportunity to study such cases, our observations having been confined to patients with either tumor or hyperplasia of the zona fasciculata of the adrenal.

Our first patient studied in 1936 had some difficulty with her teeth, which produced toothache. She had caries and pyorrhea. We had the dentists see her in consultation. They extracted two teeth forthwith, and she was dead within 48 hours from blood stream infection. When I looked over the literature I found two other similar patients who had died following tooth extraction. These people simply cannot resist infection or stand that kind of insult or "stress," if you wish. Do you think that the disturbance in the electrolyte metabolism may play a role in this?

I should like to make one other comment which concerns the hypernatremia. We found this in our first patient with hypokalemia, hypochloremia and alkalosis. That woman on admission had 158 mEq. per liter of Na. She showed adrenal hyperplasia. Another patient, an 8-year-old girl also with adrenal hyperplasia had a serum Na of 152. Two other children, showing the typical serum electrolyte changes, had 155 and 156 mEq./l. These two died from carcinoma of the adrenal cortex. But few of such patients show hypernatremia. All of these figures were found very early. As soon as we began to treat their diabetes and to do a few other things, the Na dropped to within normal before other distortions in the electrolyte pattern changed.

One other little point has just occurred to me as being worth mentioning, namely, that spontaneous Cushing's syndrome may be a transient condition in some instances. Dr. J. M. Adams and I reported one such case which we studied earlier. I saw her just the other day as a woman of 30, about 15 years after she had last been observed to recover from her temporary, postinfectious picture of Cushing's syndrome. She did not have Cushing's syndrome but only the telltale signs of healed acne and a little tendency to rotundness and shortness of stature. Her blood pressure was now normal, as was every other sign. Simpson of England has written me about a similar case, just a transient functional disturbance rather than anything profound. Such a condition as Dr. Sprague speaks of in which tumor or hyperplasia of the cortex is not demonstrable but still there is overactivity of cortical cells, might account for these cases.

DR. EDELDORF: Dr. William Schwartz and I have had a chance to observe the effects of large doses of hydroxycorticosterone, compound F acetate, by mouth in normal subjects. We find that the response of the K balance to the administration of this hormone is conditioned by the K intake in the same way as the response to desoxycorticosterone is, in the sense that, if you put a normal subject on a very low Na diet and give him large doses of compound F., there is no loss of K in excess of N. As a matter of fact, the loss of N may be far in excess of the actual loss of K; so that, with respect to any reasonable K/N ratio, one ends up after a balance period of two weeks with a relative retention of K with respect to N. On the other hand, if one gives that same subject or another subject that same dose of compound F on a normal Na intake, one observes a transient, very large loss of the K in excess of N which rapidly tapers off after about a day or two, and then, the loss of K is in proportion to the loss of N or may actually lag behind it.

We have observed with desoxycorticosterone and with compound E, cumulative K losses in excess of N up to about 200 mEq. We have observed serum K values of as low as 2.8 or 3 mEq./l in normal subjects, but, unfortunately, we have never been able to see any definite alkalosis. We feel that a large K depletion can occur even in the absence of alkalosis; we were fortunate enough to observe two patients who lost over 500 mEq. of K in excess of N due to excessive use of laxative. I believe Dr. Schwartz mentioned these patients yesterday. Not only were these subjects asymptomatic, despite loss of about a third of their body K, but their serum bicarbonate values were within the normal range.

DR. BUTLER: I wish to emphasize Dr. Flink's mention of K deficiency in Addison's disease and the therapeutic problem that it presents if a patient in Addisonian crisis doesn't promptly respond to DCA and saline. About 2½ years ago a boy entered the hospital as a patient of Dr. Talbot, with a diagnosis by the referring family physician of Addisonian crisis. Quite correctly the family physician had treated this patient for 3 days with DCA, saline, and glucose. When the patient came to the hospital the serum Na was 105, serum Cl 70 and serum K 5.3 mEq./l, and the NPN was 15 mg. per cent. To correct the low serum Na and Cl concentrations, the patient was given parenteral fluids containing Na 190, Cl 150 and lactate 40 mEq./l of 10 per cent glucose. Though the serum Na rose somewhat — if I can remember the figure, up to about 123 — the patient's dehydration did not improve and the clinical condition got worse and the hydration didn't improve because of a diabetes insipidus-like urine volume. When EKG showed a marked K deficiency, we altered the parenteral fluid therapy, providing the patient for the next 3 days with parenteral fluids containing Na from 50 to 75 mEq./l, K from 50 to 100 mEq./l and Cl from 100 to 150 mEq./l. With such therapy the metabolic defect was promptly corrected and the patient recovered nicely.

DR. DANOWSKI: We have seen 100 patients treated with ACTH and cortisone, chiefly rheumatic fever patients in the pediatric group, under 16. Balance data are available in 4 of them and support the point that was so well made by Dr. Flink. The Na content of the diet does affect the incidence of hypopotassemia. The provision of a diet which contains only 1 or 2 mEq. of Na each day eliminates, minimizes, or defers the appearance of low serum K levels. In the course of therapy of these patients it also became evident that some of the well-known metabolic effects of cortisone and ACTH do not persist. For example, these patients go into positive N balance and retain K if K and N are provided in adequate amounts in the diet. Similarly, it is very difficult

in these youngsters to demonstrate any alteration in carbohydrate metabolism.

DR. PETERS: I am going to be guilty of asking a foolish question, or at least a question that will expose my ignorance. I wonder if anyone, in line with what Dr. Schwartz and Dr. Danowski and others have said and what I spoke of yesterday, has tried to treat any of these cases with rigid Na restriction instead of giving K, and if so, what the effect of such treatment has been? In view of the known effect of restricting Na with respect to the action of DCA – and here we have heard with respect to the action of compound F – it should be quite effective in preventing this syndrome of hypokalemic alkalosis or whatever you choose to call it.

DR. GARDNER: Dr. Flink made the interesting comment that patients with congenital adrenal hyperplasia of the Na-losing type tend to need more desoxycorticosterone (DCA) than ordinary Addisonians. I think it is important to emphasize the difference that exists between the patient with classical Addison's disease and the child with congenital adrenal hyperplasia of the Na-losing type. There is good evidence now to support the hypothesis that in the latter condition, we may be dealing with a hyperplastic adrenal that is secreting a hormone which *promotes* Na excretion. Evidence in favor of that is the appearance of normal adrenal glomerulosa tissue in at least one such patient. Furthermore, it has been found that in some cases of congenital adrenal hyperplasia of the Na-losing type the administration of ACTH causes a Na *diuresis*. This would support the concept that this abnormal adrenal gland is producing in excess something which promotes the excretion of Na. Such a patient may need relatively more DCA to correct his Na metabolism than an ordinary Addisonian whose defect is a simple lack of Na-retaining hormone.

DR. ULSTROM: I would like to amplify Dr. Gardner's remark just now on the loss of Na during ACTH administration in children with congenital adrenal hyperplasia. We have repeated that and we found also at the same time that K retention does occur. Also we have noted that a greater resistance to lowering the serum K occurs in these children than the resistance to elevating the serum Na. I would also like to direct a question to either Dr. Flink or Dr. Sprague. Recently there has been a lot of interest in certain types of adrenal steroids that are excreted in abnormal states. The Allen color test, which is probably specific for dehydroisoandrosterone has been used. It has been found that patients with Cushing's syndrome on the basis of adrenal tumor excrete this substance in their urine much more regularly than those having just adrenal hyperplasia. I wonder if any correlation has been done of Na and K metabolism and the presence or absence of dehydroisoandrosterone.

DR. FLINK: I wish to thank the participants in this discussion and I am glad that Dr. Relman brought up matter of K to N excretion ratio. There is a difference between the naturally occurring disease Cushing's syndrome and the administration of hormones partly because of the chronicity of the disease. One would hardly want to administer substance to a normal individual long enough to produce all of the troubles that a patient with Cushing's syndrome has. A patient with Addison's disease who had four DCA pellets received saline and glucose solution for a number of days when she was unable to eat. She died suddenly of paralysis at a time when she had severe hypopotassemia. We did obtain CO_2 at the time and there was no alkalosis in spite of severe hypopotassemia. This was true of another patient with Addison's disease who had a respiratory infection and failed to eat, had DCA pellets, and developed hypoglycemic coma, hypopotassemia and fatal respiratory paralysis. That only some patients receiving steroid hormones develop hypopotassemic alkalosis is exactly the same phenomenon that Dr. Sprague mentioned regarding hypopotassema in Cushing's syndrome. Regarding Dr. Peter's question about restriction of Na in the diet, this has been done chiefly in an attempt to prevent the developmena of edema. From the standpoint of practical prevention of hypopotassemia patients would rather take KCl than be on a severely restricted Na diet. Except for the theoretical possibilities it is much easier to administer KCl than to restrict the Na. I will leave the last question to Dr. Sprague.

DR. SPRAGUE: I appreciate Dr. McQuarrie's comments. The terms "Cushing's disease" and "Cushing's syndrome" are frequently used interchangeably. Actually, if one wishes to be entirely accurate, the term "Cushing's disease" should be applied only to patients like those originally described by Cushing; namely, those who have the characteristic features of the syndrome and are known to have a basophilic tumor of the anterior pituitary. The term "Cushing's syndrome," on the other hand, can properly be applied to any patient who presents the clinical picture described by Cushing, regardless of what endocrine pathologic condition may be present.

It should be pointed out that not all patients with Cushing's syndrome have basophilic tumors of the pituitary, and a few have been described who did not even have Crooke's changes in the pituitary. Basophilic adenomas and Crooke's changes, when they occur, may as well be retrogressive as causative lesions. The common belief that the syndrome is usually a consequence of excessive secretion of corticotropin by the anterior pituitary never has been proved and may well be untrue. We have tried to demonstrate excessive amounts of corticotropin in the blood of patients with Cushing's syndrome but never have been able to do so, although by the method employed we did demonstrate excessive amounts of the hormone in the blood of patients with untreated Addison's disease.

On the other hand, there is overwhelming evidence that the syndrome in all cases results from adrenal cortical hyperfunction. It is not known (except in those cases in which the syndrome is attributable to a tumor of the adrenal cortex) whether the hyperfunction of the adrenal cortices is a primary condition or a secondary phenomenon resulting from a stimulus arising in the anterior pituitary or elsewhere.

I agree with Dr. McQuarrie that patients with Cushing's syndrome are remarkably susceptible to infections, including fungi as well as bacteria.

I can add little to Dr. Ulstrom's comments concerning the finding of elevated quantities of dehydroisoandrosterone more frequently in the urine of patients whose Cushing's syndrome is attributable to adrenal tumor than in the urine of patients whose Cushing's syndrome is attributable to adrenal hyperplasia. The hormonal output of adrenal tumors, as judged by the steroids found in the urine, is frequently greater than the hormonal output of hyperplastic adrenals. Dehydroisoandrosterone, as well as other beta-hydroxy-17-ketosteroids, is often found in larger quantity in the urine of patients with tumor than in the urine of patients with hyperplasia. I know of no studies indicating a correlation between abnormalities of the metabolism of Na and K and the finding of dehydroisoandrosterone in the urine.

Relationship of Potassium to "Steroid Diabetes" in General and Steroid Hormone-Induced Insulin Resistance in Particular

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ADRENOCORTICOTROPIC HORMONE, compound E, and compound F have been administered to diabetic patients as part of a study* designed to evaluate the effect of cortical steroids upon certain aspects of lipid metabolism.[1]

In the initial portion of this work, studies were of necessity discontinued after a brief period because of the rapid development of hyperglycemia in association with extreme insulin resistance (figure 1). The finding of insulin resistance under these circumstances is in accord with observations in the literature.[2]

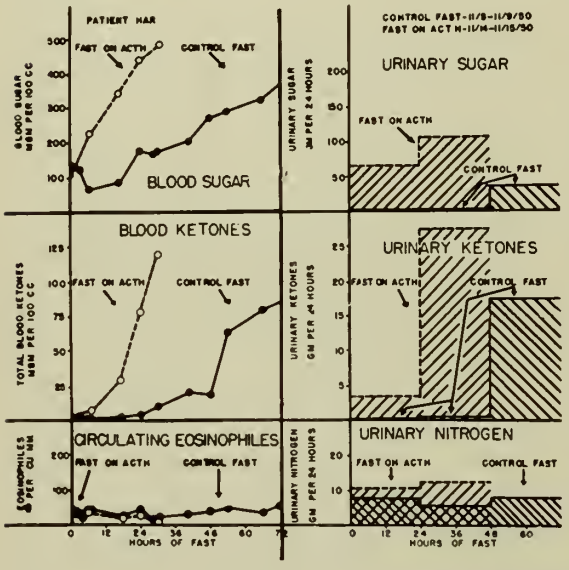

Fig. 1. "Control" and "ACTH" fasts on diabetic patient HAR. The ACTH study was discontinued after 24 hours, because of the rapidly progressing hyperglycemia, acidosis and insulin resistance. Several hundred units of insulin were required to control the ACTH-induced hyperglycemia and acidosis.

In evaluating the metabolic data in patients treated in this manner, it was noted that a major loss of base occurred during the period of development of insulin resistance, and that K loss was relatively greater than in the case of any other single basic ion measured.[1b] Since K ion was known to be associated with certain aspects of carbohydrate metabolism,[3] it was postulated that the K loss per se was responsible in whole or in part for the development of insulin resistance during the administration of ACTH and cortisone.

Accordingly, in the organization of further studies in diabetics, K was administered in relatively large amounts during the time of administration of ACTH and cortisone. Under these circumstances no insulin resistance developed (figure 2). The question arose as to whether this effect was attributable to K ion per se, or was referable merely to the prevention or lessening of depletion of fixed base. The administration of Na instead of K to patients under these conditions has so far failed to produce a comparable effect.

In a study just completed in a patient with mild diabetes in whom endogenous insulin production was still fairly adequate, the effect of K and Na administration upon steroid hormone-induced exacerbation of the diabetic state was determined. The administration of 443 mEq. of K over a period of 6½ hours resulted in a fall in blood sugar from 228 to 154 mg. per 100 cc. Repetition of this study with a smaller amount of K again produced a comparable fall. Maximal fall in blood sugar coincided with maximal elevation of serum K. On a subsequent day, when no K was administered, the blood sugar rose during the period corresponding with the fall noted with K administration. Administration of 1026 mEq. of Na over a period of several hours resulted in no comparable fall in blood sugar. These findings are shown in figure 3.

It would therefore appear that the depletion of K ion is an essential part of the total "diabetogenic" effect of cortical steroids. The precise mechanism of this effect is by no means clear, but the following possibilities must be considered:

1. Potassium prevents resistance to insulin, and/or
2. Increases sensitivity to insulin, and/or
3. Increases production of endogenous insulin.

A portion of this concept is presented diagrammatically in figure 4 (see page 224).

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*These studies were carried out with the assistance of Harry E. Balch, M.D., George D. Michaels, Ph.D., June Bilisoly, Nancy Bloomfield, George Fukayama, Eleanor Kipp, and Florence Olson.

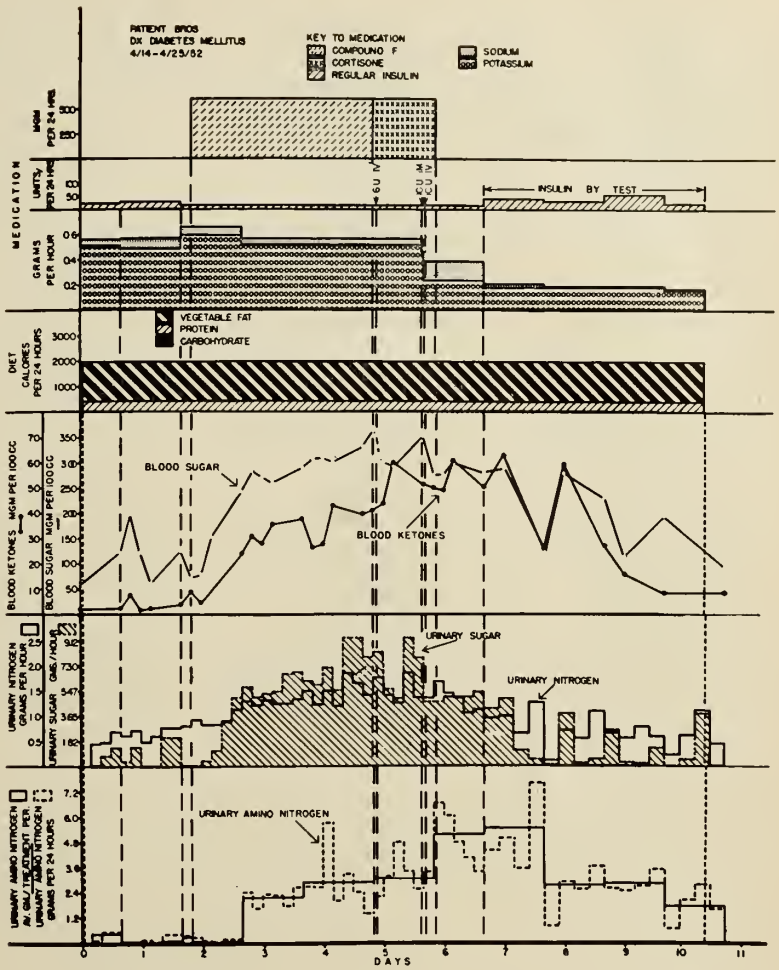

Fig. 2. Sufficient K supplementation to prevent major K depletion (despite progressive Na depletion) appeared to prevent the development of steroid hormone-induced insulin resistance.

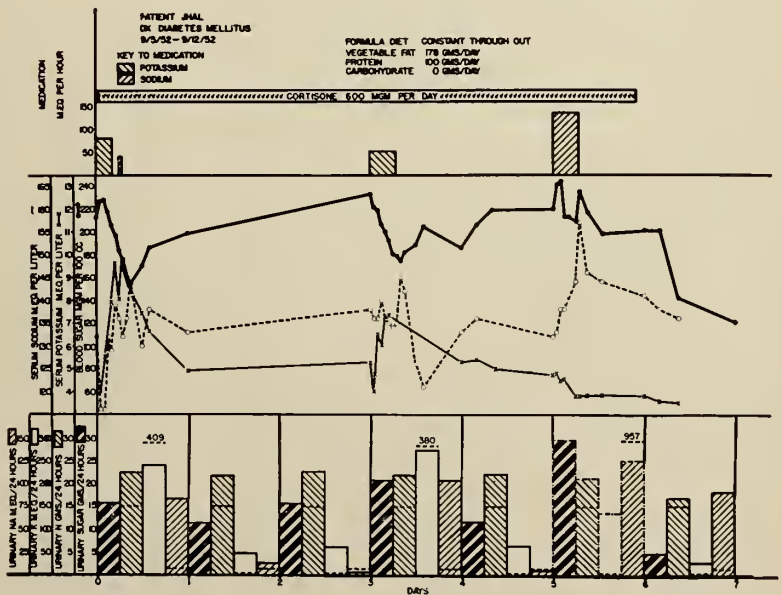

Fig. 3. K administration appeared to inhibit the diabetogenic effects of cortisone, (i. e., to cause a marked fall in blood sugar) in this mild diabetic. On the day following the second administration of K, the blood sugar rose from approximately 180 to 215 mg. per cent during the period corresponding to the fall on the previous day. The changes occurring during and following Na administration are not readily interpretable. Broken lines (Na, K, N) represent intake.

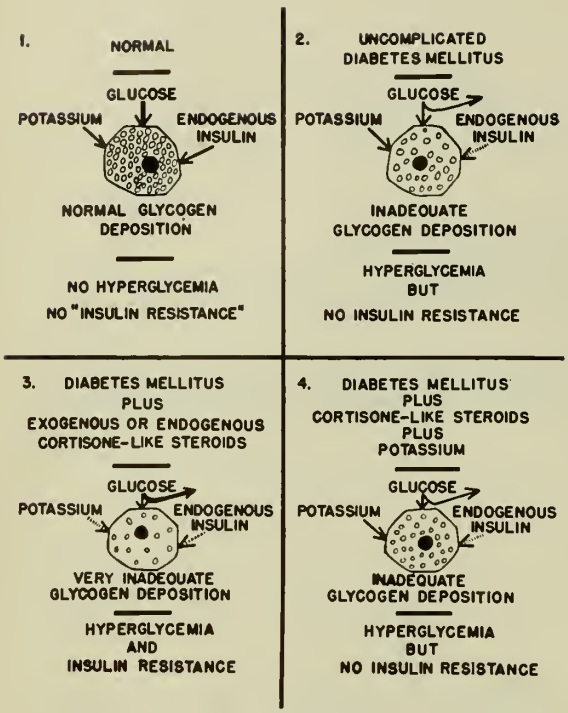

Fig. 4. Diagrammatic concept of the relationship of K to carbohydrate metabolism. It is probable that K is essential for the normal activity of enzyme systems associated with carbohydrate storage and oxidation.

DISCUSSION

DR. GUEST: Question to Dr. Kinsell. In these studies of insulin resistance, were any determinations made of serum K and inorganic P, in parallel with determinations of blood sugar? Such measurements may yield pertinent information on the response to insulin under varying conditions, as we have observed in mineral acidosis and nephritic acidosis such tests may also be valuable in studying insulin resistance developing during infectious diseases and under other conditions of stress.

DR. KINSELL: In reply to Dr. Guest's question concerning modification of insulin resistance in patient JHAL — evaluation of response to a standard dose of insulin in the same patient, at different starting blood sugar levels, makes for difficult comparison. The initial blood sugar levels in this patient prior to cortisone were approximately 90. On cortisone they exceeded 200 mg. per 100 cc. We, therefore, are able to talk only about modification of the total diabetic state by K in this patient. In severe diabetics in whom K depletion occurs rapidly when corticoids are administered, extreme insulin resistance develops rapidly. Adequate K supplementation appears to completely prevent such insulin resistance even when very high blood sugar levels are attained and maintained.

Studies in Diabetic Coma and Acidosis

Interrelationships of Urinary Potassium, Sodium and Chloride

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IN DIABETIC ACIDOSIS or coma an osmotic diuresis attributable to glucose is usually present together with dehydration. Studies in nondiabetic animals and humans under controlled conditions of hydration have established that an osmotic diuresis induced by a sugar is accompanied by an increased excretion of Na and Cl with little change in the other urinary solutes, including K. To determine whether or not these relationships prevail in diabetic coma, urine collected during more than 200 individual study periods in 47 cases has been analyzed for Na, K, Cl, carbohydrate, and N and certain correlations have been found.

A positive correlation exists between the rate of urine flow and the hourly excretion of carbohydate, Na, K, Cl, and N ("r" ranged from +0.728 to +0.795 and the "p" values indicated high statistical significance). A positive correlation was also present between the hourly output of Na and K (+0.716), and similarly, though to a lesser degree (+0.494), between urinary K and Cl.

Subdividing these data into lower and upper 50 percentiles revealed the following:

		K^+ mEq./hr.		
		Number	*"r"*	*"p"*
Na^+ (lower 50%	< 5.0 mEq./hr.)	108	+0.268°	0.01
Na^+ (upper 50%	> 4.9 mEq./hr.)	103	+0.636°	< 0.0001
Cl^- (lower 50%	< 6.0 mEq./hr.)	102	—0.249°	0.02
Cl^- (upper 50%	> 5.0 mEq./hr.)	109	+0.627°	< 0.0001

° "r" is statistically significant.

Hence at the higher levels of Na and Cl excretion a high positive correlation was present between the output of these ions and of K. At the lower levels, however, a positive but low relationship was present between K and Na in urine and an inverse correlation between Cl and K (−0.249).

Similar perusal of the upper and lower 20 percentile groups showed:

		K^+ mEq./hr.		
		Number	*"r"*	*"p"*
Na^+ (lower 20%	< 2.0 mEq./hr.)	42	0.283	0.07
Na^+ (upper 20%	> 12.9 mEq./hr.)	40	+0.629°	< 0.0001
Cl^- (lower 20%	< 2.9 mEq./hr.)	42	—0.516°	0.0005
Cl^- (upper 20%	> 15.4 mEq./hr.)	41	+0.684°	< 0.0001

° "r" is statistically significant.

Hence at low levels of Na output the excretion of this ion and of K are no longer related, a trend apparent in the lower 50 percentile subdivision. Again a negative correlation, this time stronger, is present between urinary Cl and K with low output of K, while with higher excretion rate, > 15.4 mEq./hr., a significant positive relationship is evident.

These data are compatible with but do not establish the possibility that a large output of either Na or Cl induces a large output of K. At low levels of excretion Na exerts no demonstrable effect upon K output while Cl is inversely related to it. In view of the diverse or nonexistent relationships of K excretion to either Na or to Cl output at low levels of the last two, the following findings are understandable:

		Na^+ mEq./hr.		
		Number	*"r"*	*"p"*
Cl^-	(lower 50% < 6.6 mEq./hr.)	106	—0.041	0.68
Cl^-	(upper 50% > 6.3 mEq./hr.)	105	+0.737*	< 0.0001
Cl^-	(lower 20% < 2.9 mEq./hr.)	42	—0.264	0.09
Cl^-	(upper 20% > 15.4 mEq./hr.)	41	+0.690*	< 0.0001

* "r" is statistically significant.

These data indicate that at lower levels of Cl excretion Na output is independent. At higher rates of Cl output Na is positively correlated.

COMMENT

These findings suggest that perhaps insufficient attention has been paid to the final composition of urine in diabetic coma as a determinant of the fate of administered electrolytes. It appears that a high excretion rate of any one constituent will tend to increase the excretion of others. If, for example, the intake of K is inadequate during a period of high NaCl output this relationship could be expected to produce or further aggravate deficits of K. These grouped data afford no clue as to whether the interrelationship involves renal, or extrarenal processes, or both.

The above data indicate that at lower rates of output the solutes of urine do not have as obligate a relationship to one another. Under such circumstances the usual reliance upon the ability of the kidney to make adjustments in the excretion of individual electrolytes in accordance with deficiencies or excesses appears somewhat more justifiable.

DISCUSSION

DR. GUEST: All of us who have followed Dr. Danowski's excellent metabolic studies on patients in diabetic acidosis admire the contributions he has made to our knowledge of the losses of K and other labile constituents of the body at different stages of acidosis. It is on that point I should like to talk briefly, considering the factors that lead to such losses. I should like to know whether metabolic losses within short periods of time (e. g., hourly) have been correlated with change of blood pH within the same periods. When discussing the glycolytic cycle in relation to the turnover of P and K as well as glucose, this morning I stressed the fact that there is a delicate equilibrium between processes of catabolism and anabolism, easily disturbed by shifts of pH which affect enzymatic reactions.

The factor of acidosis *per se* in diabetic coma is important, favoring the breakdown of labile constituents of the cells and inhibiting anabolic processes. Several factors in diuresis must be evaluated separately. Glucose loading in a normal subject leads to great losses of NaCl (extracellular electrolyte) without much acceleration of the losses of P, K and N; but glucose loading in the acidotic subject leads to greatly increased excretion of these intracellular elements, by the process of "washing out" elements escaping from the cells in the acidotic state. In one of his papers Dr. Danowski stated that during early hours of recovery from diabetic coma K continued to pour out of the cells. I presumed that this was observed in patients treated with insulin and salt solution and that the losses continued until insulin action became effective and pH was corrected with elimination of ketosis. I have not made similar studies of K excretion, but we did observe that the excessive excretion of P, characteristic of diabetic acidosis, ceased abruptly when acidosis was corrected by the administration of $NaHCO_3$ in conjunction with other usual fluid therapy. If such reasoning is correct, the correction of blood pH to normal (without full correction of the blood bicarbonate) may be a critical factor in restoring anabolic processes of metabolism.

DR. KNOWLES: I should like to congratulate Dr. Danowski on processing 200 urine collections. In diabetic acidosis there are so many variables that I don't think you can prove anything unless you have a large amount of data. In series where you see 10 cases of this versus 10 cases of that, I don't believe conclusions can be drawn. Dr. Danowski said that he related his urine flow very well to the sum of the Na, Cl, and K ions. In Cincinnati, Dr. Guest and I have been studying the mechanism of diuresis in diabetic acidosis. We can relate the urine flow quite well to Na, better yet to glucose, but best of all to the solute load. We believe in diabetic acidosis that osmotic diuresis is occurring in a hydropenic subject, and the urine flow is determined by the total solute load destined for excretion. The flow load curves (from 20 cases of acidosis with collection periods just before and after onset of treatment) are linear and are little to the left of the control curves in nonacidotic subjects rendered hydropenic and diuresed. Analysis of the composition of the urinary load revealed that glucose is the major constituent of the total osmolarity, and consequently is the major cause of the osmotic diuresis. In raising up the blood sugar levels with 10 per cent glucose, etc., we could get a rise in Na and Cl excretion similar to Dr. Danowski's findings. However, when you calculate the total amount put out over a 6 hour period and compare it with the amount that you are running in as therapy, this loss is insignificant. Consequently we don't believe that heavy glycosuria can cause serious Na loss during treatment. We could find no significant increase in urinary K and P during glucose loading. However, we studied only 20 patients, or 40 periods. Dr. Danowski has 200 and he shows a difference statistically. Finally I would certainly like to agree with him about the excess use of Na early in the treatment and its causing a urinary diuresis of K. I have noted that several times. In studying the use of hypertonic Na solutions, I measured the erythrocyte K levels at frequent intervals in one case. The erythrocyte K dropped 30 mEq./l. and was replaced mole for mole by Na. In K deficiency states, the forcing of Na probably extrudes yet more K and accounts for the increased urinary K.

DR. SARTORIUS: Several years ago we did studies on a similar problem, one involving acidosis in diabetic patients. In trying to determine what the kidney was doing toward restoring homeostasis or regulating electrolyte balance, we came to the conclusion from our studies that the results depended more on the time we obtained the urine and the duration of the acidosis. Thus, we found that what was more important was the capacity of these kidneys to turn out NH_3 to conserve Na and restore bicarbonate content to the blood stream. In diabetics, where the capacity of the kidney to excrete NH_4 and H ions was impaired, the body would put out greater amounts of K; hence, the acidosis would persist with this increased excretion of K. In the young there was a tendency to return Na to the blood stream and to maintain circulating base reservoirs. There is a normal lag in the capacity of the kidney to excrete H ions or NH_4 ions which is exaggerated in diabetes. In the early stage of this excretion of K and of Ca, mobilization from the bones and intracellular reservoirs plays an important role in base conservation. So, as progression of the acidosis is observed, more K is seen to be put out in the early stages, but then, as NH_3 and carbonic acid output increases under the stimulus of the lowered plasma pH, and only then, does the excretion of K diminish and the intracellular K reservoirs stay intact. Then, the body can restore the blood pH and we find diminished excretion and actually positive balance of all fixed base levels. So in the early stages we see a very strong correlation between all fixed based and water excretion by the kidney, but with compensation and with maximum output of NH_3 and organic acid, urine output falls down and we no longer see a close correlation between water output and electrolyte excretion.

DR. DANOWSKI: Deficits of total K are present as a consequence of inadequate intake, vomiting, and continued urinary losses of this electrolyte. Both extracellular and cellular K have been lost. Movements or release of K from cells have accompanied or resulted from (a) destruction of tissues as a consequence of negative N balances and gluconeogenesis, (b) deglycogenation, (c) dehydration, and (d) by analogy with isolated blood cells and interruption of carbohydrate metabolism, instead of and by blood cells. Whether or not such increments of K coming from cells to extracellular fluid result in hyperpotassemia, hypopotassemia, or only slight fluctuation in serum K will depend upon the concomitant alterations in the volume of extracellular water and the rate of urinary excretion or gastrointestinal loss of this ion. With therapy serum K levels drop, especially if K is not administered, as a consequence of re-entry of K into cells, dilution of body fluids, and continued urinary excretion of the ion.

Dr. Guest has properly pointed out the importance of early correction of the pH changes to facilitate carbohydrate utilization. This would minimize urinary losses and ultimately aid in restoring the body stores of K.

I would certainly agree with Dr. Sartorius and Dr. Knowles that there is a phase during diabetic acidosis and coma during which the kidney is not capable of making adjustments that it can make later on. Hence if there is such a limit in the kidney's ability to be intelligent in conserving necessary items such as K, can this limit be reached all the sooner if excessive solute loads, and especially NaCl, are administered?

Homeostatic Limitations in Parenteral Fluid Therapy

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BALANCE STUDIES of patients suffering diabetic coma[1,2,3] and recovering from coma[4,5,6] and from other types of dehydration with starvation[7,8,9] have defined the order of magnitude of water and electrolyte repair and maintenance needs during the first 24 hours of therapy. In the absence of some complicating factor, such as serious infection or continuing abnormal loss of body fluids, the dehydration losses approximate per kg. of body weight:

100 cc. H_2O, 7 mM. Na, 5 mM. Cl, 4 mM. K*, 1 mM. P*, and 0.2 mM. Mg.*

Repair in the first 24 hours of therapy of more than 80 per cent of these losses seems unnecessary and possibly undesirable.

In addition, the maintenance needs during this 24 hours of therapy approximate per square meter of body surface area:†

1500 cc. H_2O, 20 mM. Na, 20 mM. Cl, 20 mM. K, 15 mM. P, and 4 mM. Mg.

*Estimated loss in excess of protoplasmic loss as measured by urine N.

†While losses are proportional to body mass, maintenance needs reflect physiologic functions that correlate more closely with surface area.

For a child of 1 square meter or 30 Kg. (i. e., about 8 years of age), 80 per cent of the above losses per Kg. plus the 24 hour maintenance needs per m^2 would be in round numbers:

4000 cc. H_2O, 200 mM. Na, 140 mM. Cl, 120 mM. K, 40 mM. P, and 8 mM. Mg.

Reduced to the familiar terms of concentration pertinent to parenteral fluids, these amounts become, again in round numbers:

50 mM. Na, 40 mM. Cl, 30 mM. K, 10 mM. P, and 2 mM. Mg. per liter of water or per liter of 2 to 10 per cent solution of glucose.

Glucose is essential to arrest the starvation and further depletion of body water, electrolytes and protein, as well as glycogen and fat, except in the initial phase of diabetic coma therapy. Here an osmotically disturbing hyperglycemia already exists which provides glucose for oxidation by the insulin administered during the first few hours of therapy. Consideration of the accuracy of such approximations of repair and maintenance needs is hardly worthwhile for each patient will have his particular requirements and at present there is no way to ascer-

tain them promptly. Clinical appraisal by history and physical examination and determination of serum and urine concentrations provide but rough guides.

In the absence of accurate knowledge of specific requirements, an important consideration in repair therapy is provision of water and solutes midway between the patient's minimal requirements and his excretory tolerance. This permits the patient the maximum leeway in retaining what is needed and excreting whatever is in excess of needs. Too often doctors by prescribing therapy that overtaxes normal homeostatic functions fail to take advantage of the wisdom of the patient. The value of utilizing such functions becomes striking when dealing with patients who suffer such limitations in homeostasis that they are dependent entirely upon the wisdom of the doctor. In current practice consideration of limitations in the body's ability to handle what the doctor orders is of more importance than the detail of repair needs. Of course in practice the limitations of each patient's homeostatic mechanisms must be continuously appraised. Fortunately, there are increasing techniques for so doing, including the techniques for promptly following renal excretion, the importance of which has just been so nicely emphasized here by Dr. Danowski.

Figure 1, constructed by Dr. Nathan Talbot, permits a concise review of such considerations.[10] It shows the relations between the electrolyte content (expressed as milliosmoles per liter) and the volume of intravenously administered glucose solution and change in body water concentration (expressed as cubic centimeters per milliosmole) of normal persons and of stressed patients.*

In constructing the figure water balance has been defined as:

H_2O bal. = H_2O I.V. + H_2O of oxidation and tissue oxidized − insensibel H_2O − urine H_2O.

Insensible H_2O has been taken as 1000 cc./m^2/day; H_2O of oxidation and H_2O content of tissue oxidized as 270 cc./m^2/day; and urine H_2O as m-osm. excreted/day ÷ m-osm./cc. urine. The m-osm. excreted/day have been estimated as the sum of: (1) the 200 endogenous catabolic m-osm. presenting for excretion in patients receiving at least 75 g. glucose/m^2/day and without glycosuria;[11,12] and (2) the m-osm. of urine solutes required to equate solute excretion with infusion solute intake.

*The equation derived by Dr. Daniel Clement is:

$$V = \frac{[(I.W. - W\,oX) + S_E\gamma)]\ 1/\gamma}{\frac{1}{\gamma} - C}$$

V = vol. fluid infused cc/m^2/doy
I.W. = insensible H_2O loss, cc/m^2/doy
W. oX = cc/m^2/day
SE = endogenous urine solutes/m^2/day
γ = urine H_2O conc. cc/m-osm.
C = inorganic sol. conc. of V., m-osm/cc.

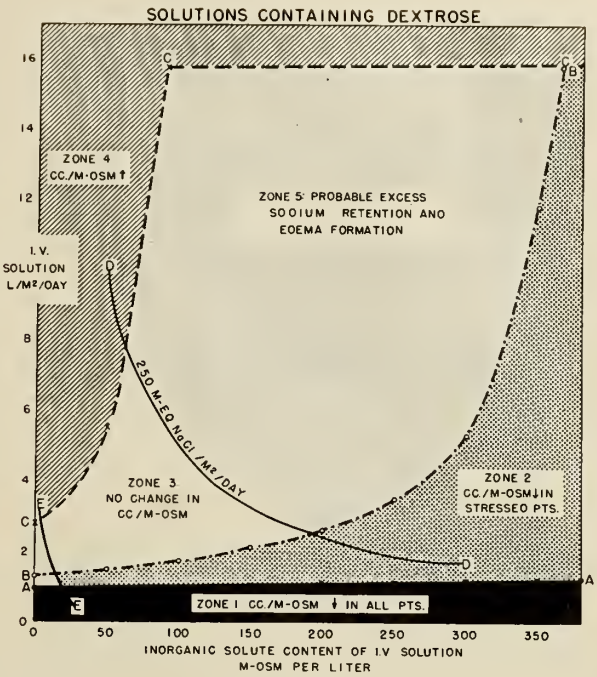

Figure 1.

One may object that we are concerned with patients for whom a state of equilibrium does not pertain because their well being depends upon retentions for repair of dehydration and solute depletion. This, as mentioned, is cared for by the wisdom of the patient, if the doctor gives him a chance.

Line A—A denotes the minimal volume of intravenous solution of varying m-osm. concentration required to keep the patient's concentration of water/m-osm. from falling in spite of maximal conservation of water by renal excretion of only 0.7 cc./m-osm. Infusions of lesser volumes result in a fall in concentration of body water/m-osm (zone 1), i. e., in dehydration.

Line B—B similarly denotes the minimal volume of intravenous solution required to prevent decrease in water concentration of the stressed patient whose ability to conserve urine water may be limited to 2.5 cc./m-osm. Thus, the area of zone 2 indicates a fall in cc. body H_2O/m-osm., or dehydration of the stressed patient.

Line C—C denotes the upper limit of water tolerance for solutions containing from zero to 80 m-osm./liter. Above this solute concentration, maximum urine volume is no longer dependent upon the maximum dilution of urine to 10 cc./m-osm., but upon the ceiling of renal water excretion of 15 liters/m^2/24 hours. Zone 4, therefore, demarcates the area of increase in cc. of body water/m-osm., i. e., of water toxication.

Line D—D demarcates the area above which infusions of saline corresponding to the abscissa concentrations result in salt and water retention and

edema (zone 5). The selection of 250 mEq. of Na or 500 m-osm. of NaCl as the limit of physiologic Na tolerance of sick patients is somewhat arbitrary but pretty well substantiated by experimental and clinical observations. Though greater attention must be given to the possibility of acute toxic effects of K than Na, the limit of physiologic K tolerance for patients not in shock or handicapped by marked limitations in renal function appears to be somewhat greater than Na.

Line E–E denotes the Na intake that meets minimal Na excretion.

Zone 3, therefore, indicates the volume and concentration of solutions that can be used with safety to meet the needs of dehydrated patients who suffer no specific defect in homeostatic function. It can be seen that 4 liters of a solution containing 100 m-osm. or 50 mEq. of total base per liter provide total solutes sufficiently above maintenance needs to permit repair of dehydration unless there is a continuing large abnormal loss of water and solutes. This has been verified by the experience of our clinic during the past 6 years.[7,10]

The graph suggests that the administration of solutions containing more than 200 m-osm. or 100 mEq. total base per liter to the stressed patient may result in either dehydration or edema. This and clinical experience indicates that isotonic saline (300 m-osm. or 150 mEq. total base per liter) should be used with more caution than is generally practiced. The graph also indicates that more than 2800 cc./m^2/day of glucose solution without electrolytes may overtax the patient's ability to excrete water and thus cause water intoxication. If ability to dilute urine has been limited by such a drug as morphine, 1500 cc./m^2/day of such a hexose solution may exceed water tolerance and cause toxic symptoms.

It is, of course, well known that "physiologic" or "isotonic" saline is not "physiologic" in any "physiologic" sense. Its isotonicity to blood in a test tube and to body fluids in vivo are very different things. In the latter, water without salt may leave the plasma promptly to meet insensible water loss, cell water repletion and urine water requirement, thus leaving hypertonic Na and Cl to be disposed of by a patient who is short of water. The biochemists present might also add that "normal" saline is not normal according to chemical definition.

In this symposium where so much importance has been placed on the role of the predominantly intracellular electrolyte, K, mention need not be made of its importance in parenteral fluid therapy. The ratio of Na to K administered in parenteral fluid therapy perhaps deserves more emphasis than accorded it by many physicians, for the ratio of commonly used solutions may be so high as to limit the retention of administered K. In our experience both in diabetic acidosis and hypochloremic-hypokalemic alkalosis, K in addition to that provided by the multiple electrolyte solution mentioned above may be required.

Finally, it is pleasant to call attention to the general agreement between the amount of solutes designated by estimation of repair and maintenance needs and the amounts indicated within the upper limits of "safe" zone 3 solutions. Moreover, the provision of a volume within the "safe" zone of such multiple electrolyte solutions as designated above does not exceed the limits of tolerance for any individual electrolyte except when patients are in shock or suffering from some other specific limitation in homeostatic function.

One may conclude, therefore, that multiple electrolyte solutions containing between 100 to 160 m-osm. or 50 to 80 mEq. total base per liter are more "physiologic" than isotonic NaCl solution. The administration of 5 per cent glucose or "isotonic" saline to patients with but little limitation in homeostatis functions may result in muscle weakness, respiratory and cardiac failure and death. Unfortunately, a stock solution of "hypotonic multiple electrolyte solution" may be inappropriate for patients with marked homeostatic disability. Thus, though advancing knowledge has simplified and improved the therapy of the average dehydrated and depleted patient, much remains to be learned concerning optimal parenteral fluid therapy for many of our most seriously ill patients.

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DISCUSSION

DR. PETERS: I would like to thank Dr. Butler for having emphasized the fact that there are more than two solutions to be used. I want to thank him in particular for emphasizing so strongly the fact that isotonic saline solution or this in 5 per cent glucose solution are not the only ones that should be available. I thank him for his diagram also because it points out the harm that might come from drowning patients internally. I think, however, that one must consider the mixtures he is talking about are the kinds that are meant for maintenance. Unfortunately a large proportion of patients we get present not merely problems of maintenance. Sometimes their disease has so distorted the internal environment

that there may be need for Na, K, Cl, NH_4Cl or all kinds of things. Under these circumstances we must be as versatile as possible in finding out what happens.

What is unfortunate is that very often the patient you have to treat presents a problem that I don't think has yet been mentioned here, a problem in which there has been a distortion of volume already and also of concentration, to such an extent that the treatment has to be a compromise. We are sometimes confronted with a patient who has been almost drowned with glucose solution. We find ourselves under the necessity of giving 3 per cent saline, which is much less normal than the so-called "normal saline" and I think that the patient has usually been given these solutions against which Dr. Butler has protested, isotonic saline and glucose, prior to seeing him. That has made people say saline is very dangerous. Certainly it is when you are flooding people and when you try to correct the kind of disturbance in which there has been partial drowning with glucose solution in saline you are only making a bad matter worse.

Again, I would like to say that after getting a patient into the condition in which one can maintain him there is too much tendency to think that he has to be forced to excrete 4000 cc. of urine a day by use of these ordinary solutions instead of using moderate amounts. I remember recently seeing an old lady who was very tired, and lacking in sleep but who was getting along very well. She was excreting only 600 cc. of urine a day and not taking much more obvious fluid than that. I saw this poor old dear being infused and I said to the intern "Why are you doing that?" He replied, "She's only getting rid of 600 cc. of urine a day and yesterday she drank only 600 cc." Well, when I inquired about her blood NPN, he said, "Why, it has been normal; it was quite low; it was 23." I said "Her kidneys are getting along all right; why torment her and prevent her from eating food." This comment is perhaps utterly irrelevant, but it is merely another way of thanking Dr. Butler.

DR. DARROW: Butler's diagram is rather confusing when first observed, but I am sure a little study will clarify its meaning. I personally would think it is unlikely to be useful in practice. However, it should prove very valuable in defining the limits of water and electrolyte intake to which the body can adjust physiologically. I cannot see how these limits can avoid other methods of calculating therapeutic requirements of water and electrolytes. Therapy involves first, replacement of deficits which are related to body weight and not rates of turnover. For this reason I believe the initial replacement must be related to body weight and disturbances in body composition. I am sure we have to consider changes in concentration and probable losses in the first phase of a plan of therapy. Butler's and Talbot's diagram defines rates of expenditure in terms of surface area. This is a correct unit of reference but since one is interested in total metabolism, surface area is likely to seem to give a precise answer when other factors which increase or decrease total metabolism must always be evaluated. In addition, one has to consider to what extent abnormal expenditure of water and electrolyte modifies the rates of expenditure indicated by the total metabolic rate.

The diagram brings out well certain facts long known by workers in the field of water and electrolyte metabolism. First, physiological saline and similar solutions should be considered primarily as means of giving Na and Cl and not water for expenditure. However, saline solutions may properly be used to replace deficits of water containing the ions administered or to provide the small amount of ion expenditure in normal subjects or the large amounts when there is abnormal expenditure of electrolyte.

Second, glucose solutions are a means of giving water for expenditure. The therapeutic problem is to plan administration of a mixture of water, Na, Cl and K and other ions so as to overcome body deficits and meet normal and abnormal rates of expenditure. I am sure that therapeutic requirements cannot be met in all cases by a system based on physiologic limits of expenditure that do not consider also the deficits and abnormal expenditure.

DR. LOWE: We have been using a solution much like the one that Dr. Butler suggests and we find it a particularly useful one for almost every type of patient. I know that the use of a single solution for all types of patients contradicts the axioms that he has presented, those which Dr. Peters presented, and I think perhaps those to which Dr. Darrow alluded. However, we have found that a solution of this composition can be used with considerable safety in almost all patients. There are, however, two exceptions: First is the patient that has some sort of central nervous system disease. Now I say, "some sort," since we have seen this problem in several different types of central nervous system disease. These patients are apparently extremely diluted with respect to serum Na, Cl and CO_2 concentrations, and do not respond to solutions of the sort mentioned by Dr. Butler. The second type of patient is that suffering extraordinary losses such as through an ileostomy or with acute ulcerative colitis. The demands of those patients cannot be supplied with solutions as dilute as the ones mentioned.

There is one respect in which our regimen differs with that suggested by Dr. Butler. That concerns the total volume of dilute electrolyte solution administered in each 24-hour period. We have found that roughly 2400 cc., for a maintenance volume of fluid, and approximately 300 cc. for an initial period of hydration and replenishment is more than sufficient for most patients and our estimation of sufficiency is derived both from a collection of material such as urine, to get a rough estimate of balance, and secondly, from the behavior of the various electrolytes in the patient's plasma.

I can only finish by echoing Dr. Darrow and feeling somewhat confused by the sight of Dr. Butler's chart on the screen. I feel that Dr. Butler has been so effective in teaching physicians about problems of fluid therapy without the benefit of this chart that I would like to ask him what contribution it offers.

DR. WILDE: I mentioned yesterday that our work with K^{42} and the earlier work with injections of chemical K (J. Biol. Chem. 128:309, 1939) have a bearing upon what is a safe rate of injection of K to prevent symptoms of toxicity during therapy.

Unfortunately, there is no body depot for K where it may be stored quickly and in nontoxic form during intravenous injection into the patient. However, as judged from its volume of distribution, injected K does spread initially into all body water equal to 70 per cent of body weight. This mimics the Boyle-Conway theory according to which K moves across cell surfaces in the form of the salt KCl. Relatively early changes in plasma concentration follow the theory. It seems plausible that the cation first moves into the free water of tissues generally by a diffusion process involving minutes.

After longer periods, measured in hours, it may accu-

mulate on fixed anionic sites in tissue cells because of special biochemical mechanisms of uptake or of synthesis of new anionic radicals. The ultimate effect of these latter mechanisms upon plasma concentrations of K is unpredictable and must be estimated by flame photometry or electrocardiographic changes.

One must then predict the initial amount of dosage entirely by the Boyle-Conway theory. If in a one kilo patient one wanted to elevate plasma K, that is K in total body water, + 1 mEq./liter, one would inject 1 $(1 \times .7) = 0.7$ mEq. K/kg. of body weight. Multiples of this would give correspondingly higher plasma elevation.

This may be injected in two stages: a fast stage representing movement from the blood stream into the interstitial fluid followed by a slower stage involving movement into tissue cell water. In the first or transcapillary stage *excess* plasma K^{42} declines at the rate of 225 per cent per minute in the rabbit and *excess* plasma K at the rate of 190 per cent per minute in the cat. Since the correct rate for man is unknown, we will use the latter figure in our illustrative example. We have elected that the maximum excess concentration of plasma K be kept at + 1 mEq. per liter during the injection.

At this concentration there would be contained in the total plasma, as a volume, 1 (1×0.05) or 0.05 mEq. K, the maximum mass of excess K allowed in the plasma. Of this, $0.05 \times 1.9 = 0.095$ mEq. leaves each minute. The latter would be the injection rate but this may be kept up only until the extracellular fluid is equilibriated with the plasma both at a concentration of 1 mEq./liter. Since the extracellular fluid amounts to about 30 per cent of body weight, our total dose at this fast rate would be 1 $(0.3 \times 1) = 0.3$ mEq./liter. This dosage must end after 0.3 mEq. has been injected which would require 0.3/0.095 or 3.16 minutes.

There remains $0.7 - 0.3 = 0.4$ mEq. yet to inject but this will move from extracellular fluid into cellular water at a slower rate of 3.5 per cent per minute of the excess in this fluid (second stage in the cat). The excess allowable in this compartment is, of course, 0.3 mEq. This will move out into the cells at the rate of $0.3 \times 0.035 = 0.0105$ mEq. per minute, the maximum injection rate allowable during this second phase. This would continue on through 0.4/0.0105 or 38 additional minutes to complete the total administration.

Any K-depleted patient has a deficiency in "biochemically" stored K as well as in this Boyle-Conway type K present free in the body water. Thus, the biochemical mechanism will begin to use up this initial dose. In subsequent hours further K will need to be injected or fed, according to the condition of the patient. The immediate elevation in plasma K to be expected from a given dose will always follow the Boyle-Conway rule, regardless of the level of biochemical storage. Thus, the rule constitutes a safe maneuver for later dosages, which might be repeated, say every two hours, until the flame photometer or EKG indicates from the plasma level that biochemical storage is completed.

DR. BUTLER: Dr. Lowe has answered some of the comments of Dr. Peters and Dr. Darrow. Dr. Peters seems to have missed the point of my nice simple diagram. This astonishes me. The point is that 3–4 liters of a solution containing around 40 mEq. of Na, 35 of K, 45 of Cl, 20 of biearbonate or lactate and 15 of phosphate per liter will repair dehydration in the patient who is not having a continued abnormal loss. Our proof of that during 6 years of such therapy in rehydrating severely dehydrated infants, children and adults has been supplemented by Dr. Lowe's remarks. Dr. Darrow commented that he didn't think this graph has much practical application. To this I'd like to comment pleasantly but emphatically: It is the most practical application of existing knowledge concerning the provision of repair and maintenance therapy that I have yet encountered, admitting, of course, that I may be ignorant of what's available. Dr. Lowe wants to know what the chart can contribute. Well, it ought to contribute to Dr. Lowe's confidence, that in using solutions indicated by the graph to be physiological, he has been doing the right thing.

DR. PETERS: I would like to answer another point brought out by Dr. Butler. Someone asked whether he was speaking about children or adults. In adults K may sometimes change without becoming evident in analyses of the serum; but electrocardiograms may also change as a result of disease in such a manner that they have the appearance of the electrocardiograms of K deficiency.

Disturbances of Potassium Metabolism Associated with Chronic Disease and Surgical Procedures

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IN ACCEPTING Dr. McQuarrie's kind invitation to participate in this conference, there was the clear reservation that my factual contributions to a symposium on K metabolism would be meager; but a great interest in the subject and a fair sized experience with K-depleted patients have raised questions, the answers to which by members of this group might be helpful to physicians in dealing with clinical problems.

Our interest in the subject began about 1942 or 1943 when, together with others in a group collected by the Macy Foundation, balance studies were being made on traumatized individuals in various states of nutrition. The increased protein catabolism following injury was under particular scrutiny, and the lesser losses of N suffered by undernourished individuals as compared with those of vigorous and well nourished persons were clearly defined.[1] Along with N, the movements of other constituents of protoplasm were followed in these balance studies. It became apparent that, in general, the outward movement of N, K, P and S ran quite parallel during the protein catabolism response to injury — i. e., negative balances of these constituents were quite in keeping with their relative proportions in muscle protoplasm; for each gram of N approximately 2.5

mEq. K and 1/15th gram of P were lost. In the first few days after the trauma, K was lost in slightly greater proportion than the others.[2] Such proportional losses of intracellular constituents had also been found in starvation by Benedict,[3] by Gamble, Ross and Tisdall[4] and in our own studies of graduated underfeeding.[5] But of great interest was the fact that during repletion following either abrupt or gradual starvation, as well as *after* protein catabolism reactions, the element K was found to be retained earlier and in greater proportional quantity than were either N or P.[5]

Up to this point our experimental observations were all carried out with oral feeding. When new experiments were begun using total intravenous feeding[6] (because of the great simplicity in making balance studies due to cessation of stools), K was added to the pabulum of all our intravenously fed patients, approximately 5 mEq. per day. But we were slow in becoming aware of the possibility of K *depletion* as a clinical entity. However, in 1945 the following facts assembled themselves in proper order of cerebration—(1) McCollum's studies of rats on K-deficient diets showed that without this element death ensued; (2) Follis found necrotic lesions in the myocardium and degeneration in the kidneys of these animals; (3) Darrow found that K depletion (regardless of how brought about) was reflected in lowered serum K after a certain state of intracellular K had occurred and that a high serum bicarbonate and low Cl accompanied this state; (4) that gastric juice contains normally 3 to 5-fold the concentration of K compared to serum;[7,8] (5) that NaCl in excess tends to increase the urinary excretion of K.[9,10]

Our first experience with intravenous administration of K as a therapeutic agent against cellular depletion of this element was in patients emerging from diabetic acidosis. The enormous quantity of K accepted by the cellular compartment, apparently with great benefit, then caused us to seek other types of situations in which K depletion might exist. Undernourished individuals who required surgical operations and were then postoperatively given only NaCl and glucose solutions were watched for signs of hypokalemia and instances were soon found. The easiest way to spot them was by the otherwise unexplained presence of high serum bicarbonate and low Cl, the Darrow phenomenon, and by the electrocardiogram.

The response in these cases to the substitution of KCl for NaCl in their intravenous mixtures was dramatic. This particular individual had been ill for a month prior to hospital admission; there had been severe abdominal pain and he had eaten but little with resultant large weight loss. Exploration disclosed pancreatic necrosis with abscess formation, perforated gallbladder and infarction of the omentum. After operation practically nothing could be taken by mouth and for 21 days he was fed parenterally with glucose, saline, whole blood and plasma. A Wangensteen tube with suction was used for a part of this time. More than 6000 mEq. of Na were administered during this period. At the time we first saw him the serum CO_2 had risen to more than 45 mEq. and the Cl was down to 80 mEq. Serum K was below 2 mEq. and there were typical EKG changes of hypokaliemia together with marked muscle weakness and reduced peripheral reflexes.

On administration of KCl intravenously (small doses were used as this was one of our early cases), the EKG rapidly returned to normal, the reflexes became brisk and the patient felt and looked greatly improved. This clinical sequence could be duplicated many times over, I should like to emphasize particularly several points in this case:

1. The slowness of response in serum Cl and CO_2. It was not until the fifth day that bicarbonate began to fall and Cl to rise, and it was 10 days before their concentrations reached average normal values.

2. Likewise serum K did not reach a *stable* normal concentration until the ninth day. While the solution of K was actually running in, the serum K was of course higher than its initial level; but when the intravenous would stop, say at night, serum K would rapidly fall again in a matter of a few hours. These two observations recurred again and again in our cases and led to the impression that in this type of hypokaliemia the cellular stockpiles of this element are low and that it takes large quantities of K given over prolonged periods of time to replete such stockpiles to a point where the cellular compartment will again take over its normal function of supporting K homeostasis. Likewise the abnormal serum concentrations of Cl and CO_2 quite accurately reflect the intracellular state of K and reach normalcy at just about the same time that the cells will again (for a time at least) maintain normokaliemia. Whether or not this simple explanation truly reflects the underlying reasons for the observed facts, it is worthwhile for the clinician to be aware that, when hypokaliemia is seen in severe cases of depletion at least, a small injection of K will not do the trick, and that he must often maintain his therapy for prolonged periods before restoration of normal electrolyte values occurs.

I should like to call attention to one other feature, which we have likewise observed in other cases of this kind and which may be of even greater physiological interest. From the time of operation until K therapy was begun, there was hypoproteinemia – between 4.5 and 5.5 per cent total protein – despite the administration of 8000 cc. of whole blood and plasma over the 3 week period. No more blood or plasma was given after K therapy started, yet when K and Cl and CO_2 reached normal concentrations, the plasma proteins likewise returned to normal. It is hard to escape the belief that restitution of normal cellular electrolyte had somehow induced the motivating powers of the cellular compartment to take over again their function of serum *protein* homeostasis – a function they had formerly been unable to assume.

Our assigned subject calls for a discussion of K disturbances only in the undernourished patient and after surgical procedures. We have not observed the phenomenon of hypokaliemia, at least to a clinically recognizable degree, after surgical procedures in the seemingly well nourished patient; though this phenomenon has been observed by others[11] and attributed to hypersecretion of adrenal corticoids in response to the surgical trauma. We have been struck, when viewing their charts, with the small quantities of K which were required to restore and maintain the serum K in their patients, in contrast to most of ours.

In our group also we have seen no cases of hypokaliemia that we could attribute to inanition alone. Always there has been diarrhea, vomiting, prolonged use of gastric suction, pancreatic or duodenal fistula or some other cause of large loss of enteral juices. It is our belief, therefore, that such losses constitute the *major* factor in the production of the syndrome in this type of case. It has been our experience that gastric juice contains K in concentration three to five-fold that of serum,[8,12] and the only instances in which we have found gastric juice K below 10 mEq. per liter were in patients who coincidently were either markedly hypokaliemic,*[13] or greatly depleted generally.

The role of excess administered Na in the production of K depletion has been a source of puzzlement to us. When we tried to produce the syndrome in dogs by total intravenous feeding, as much as 18 g. NaCl and 100 g. glucose were given daily for a week. (Dogs are notoriously resistant to large salt loads.)[14] Hypokaliemia did not result and only about 70 mEq. K deficit occurred over the 7 day period. Hypokaliemia *did* result when the same treatment was given to dogs previously starved for 10 days. However, serum Cl was *elevated* and CO_2 reduced in contrast to the Darrow phenomenon so uniformly noted in our clinical cases.

In regard to this matter of excessive Na "washing out" K, a recent lecture of Dr. James Gamble, which I was privileged to read, points out some interesting data on early observations and speculations.

In 1873 Bunge, the German physiologist, noted that a large addition of K to dietary intake caused a loss of Na from the body which was approximately equivalent to the extent of K retention. And, the other way around, a Na gain from increase of intake was accompanied by a loss of K. Bunge began his experiments because of the observation, probably very ancient, that herbivorous animals (whose intake is high in K and low in Na) constantly seek salt, whereas carnivorous animals do not. Hunters, trappers and Eskimos who live almost entirely on meat value the blood highly, because here is their source of Na.[9] Recently, Leaf, Couter and Newburgh[10] demonstrated the effects of large intakes of NaCl and Na citrate on healthy adults. With NaCl the losses of K were minimal; with Na citrate K losses were sizable but nowhere near the equivalence of the retentions of Na.[10]

It would seem to us that the magnitude of the role played by excess Na intake in causing K depletion is variable, and those factors which allow Na to promote increased K excretion need clarification. This point is of great clinical importance, because one always wonders whether or not to give some NaCl along with the K, since so often there is evidence of reduced volume of *both* extra- and intracellular compartments.

We had another case, which was much like the first, except this patient's difficulties arose from a violent diarrhea which followed a colectomy; and in this instance we gave both NaCl and KCl in our total intravenous feeding mixture. There was a striking rise in serum protein concentration that occurred coincident with stabilization of serum K and restoration of Cl and Co_2 to normal. She, too, had had blood and plasma prior to K therapy, but none thereafter.

We were fortunate in this instance to obtain complete balance data during the K therapy period. The positive balance of K was quite striking and Cl likewise, but there was certainly no Na loss – indeed the balance for the two week period was nearly 200 mEq. positive. Surely in this instance, judging by the patient's rapid improvement, the administration of Na did not appear to be harmful. It should perhaps be mentioned that Na was given only because in this series of experiments we were using "Amigen" and the only Na administered was that which the Amigen contained.

In viewing the K depletion syndrome in chronically ill patients, we have usually premised the fact (following Darrow) that intracellular K is to some extent at least replaced by Na, and that in the intracellular organization substitution of Na for K results in decreased functional capacity.

From Benedict's data, our own, and those of our colleagues in the "Convalescence Study Group," simple starvation would not appear to cause a loss of K in excess over other protoplasmic constituents; and though K is accepted by cells prior to and in greater quantities than the other constituents early in the repletion phase, some other factor than simple undernutrition must come into play to produce the clinical picture which we call the K depletion syndrome. How much adrenal overfunction or excessive salt administration play in its induction is not clear, but excessive losses of enteral fluids are surely a potent force in this direction. Dr. Patricia McIntyre, in reviewing the cases of K depletion seen at Johns Hopkins during therapy of tuberculosis with para-aminosalicylic acid (and the incidence of K depletion syndrome in this series was quite high) could find no instances in which vomiting or diarrhea had not been prominent features of the clinical course.[15]

I should like to bring up now some of the questions that have arisen during efforts to formulate some sort of picture of what is going on in the cells

*Saemundsson's finding[12] of low concentration of K in gastric juice of patients recovering from diabetic acidosis may have been due to coincident low serum K.

of individuals to whom K has been administered therapeutically. The idea seems current that work is required to get K into and out of the intracellular compartment, that K enters in the form of a hexose phosphate complex, and that once it is inside the K has no ready access to the exterior. It seems to us that at least some of the intracellular K must be much more mobile than is implied in this concept. When salts of K are administered intravenously to normal dogs (and orally nearly all is absorbed),[16] a very large increment is disposed of with little or no change in the serum K and with a subsequent lag period before excretion is complete and balance equilibrium is reestablished. Contrariwise the artificial kidney experiments using K-free solutions have shown that very large quantities of K can be removed (more than the entire extracellular compartment contains) within a few hours with but slight fall in serum K and with quick restitution to normokaliemia when the experiment ends.[17] This can only mean that the cellular compartment has furnished the necessary K for this rapid homeostatic action. Thus some cellular K, somewhere in the body tissue, is accessible and available for immediate provision to the extracellular fluids should their concentration fall. One visualizes some cellular K in the peripheral part of the cell as being in ready equilibrium with extracellular K and also probably in equilibrium with the bulk of more medially situated K in the cells.

The quantitative aspects of cellular acceptance of K is of great interest. An experience of ours some years ago may be worth noting. In a patient with diabetic coma, after insulin had begun to make carbohydrate utilization apparent, K was begun by vein. Response of the hypokaliemia was so slow that we decided to see just how much this patient could accept and kept increasing the dose of K (the patient was kept constantly hooked up to the cardioscope) so that 367 mEq. K were given over an 18-hour period; only 50 mEq. were recovered in the urine and yet serum K was constantly below normal.[18]

One wonders also just what is the role of phosphate in transport of K to and from cells under circumstances of these kinds (heavy K loads and rapid depletion). It has previously been pointed out that in recovery from starvation K taken up by the body cells as a whole sooner and in greater quantity than is N or P, the latter two seeming to move in and out pretty much together. Should we provide inorganic P in our solutions when we give K intravenously, and if so how much?

Among other questions that puzzle us are these:

1. How does it happen that the neurological manifestations (peripheral motor palsies) are identical, or at least not clinically differentiable, in hyper- or hypokaliemia?

2. Are the cardiac manifestations of K depletion due solely to alterations in electrical potential and hence due to an altered *ratio* inside to outside, or can one have EKG manifestations of K depletion without hypokaliemia? We haven't seen such, but others have so reported;[19] and it seems worth clarifying this point, if the information is available among members of this group.

3. Are glucosides of the digitalis family especially toxic to patients suffering with K depletion? In an analysis of diabetic acidosis deaths which occurred prior to recognition of hypokaliemia, a number of records were found in which digitalis administration seemed to cause rapid deterioration of an already bad situation.[20]

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DISCUSSION

DR. ZIMMERMAN: I wish to express my appreciation for this very excellent paper of Dr. Howard's which answered several questions for me. We have been puzzled by a number of things. One of them is the factors which underly the development of K depletion in surgical patients. Why should some develop K depletion and others not? I think we have seen patients who have developed the entire picture of hypokaliemic alkalosis who have not had vomiting or obstruction or diarrhea. And in most instances it has been difficult to put our finger on just what preoperative situation in these individuals could predispose to their development of K depletion where the vast majority of the people do not get it. One thing has occurred to me and I am sure you have seen it too. In a number of cases there has been previous recent surgery and this is, of course, an obvious type of precursor. If the patient has a surgical operation which was preceded by a surgical operation within one week or two weeks, it seems to me they are very prone to the development of the typical picture of hypokaliemic alkalosis. A patient, for example, who had an amputation for arterial occlusion and 10 days later had a laparotomy for mesenteric arterial occlusion went into profound alkalosis within 24 hours after surgery.

Treatment with ACTH and cortisone preceding surgery has been followed by an increased incidence of

the syndrome. This, of course, one might expect. I only want to emphasize what Dr. Howard said about the long duration of K therapy which is required in some people. Bicarbonate will not respond very frequently within a matter of a few days and sometimes it takes some courage to stick with the diagnosis and resist people who want to give NH_4Cl, and so forth. I think also, although we have not collected our data on this matter, that Na excess in some people has thrown them into this situation. I have seen two or three people in whom a very low serum Na value was found shortly after operation accompanied with symptoms suggestive of water intoxication. These people were then given large doses of hypertonic NaCl solution. The Na responded rapidly and, then, within another day or so there developed severe alkalosis which would respond only to K treatment.

DR. CANNON: I would like to make some comments about the paper presented by Dr. Howard. He pointed out that in his early work in total intravenous feeding, using Amigen as the protein hydrolysate, he added K to his solutions although he did not know at that time that there was any particular reason why this should have been important. His statement was especially interesting to me because, although the manufacturers have put a great deal of money into the development of these hydrolysates, at least some of them did not know until comparatively recently that the products were deficient to some extent in K. They have now added K salts to their products in at least two instances that I know about. The earlier experiences with total parenteral alimentation, which have resulted in some discouragement and skepticism, may now be more clearly understood in relation to the lack of K. Certainly the products now available have been made relatively safe to use in terms of toxicity and lack of pyrogenicity. The use of disposable tubing has helped materially in this respect. It may be, however, that the handicaps of both caloric and K inadequacy, can account for the lack of completely satisfactory utilization of the amino acids in the hydrolysates. We found when we fed protein hydrolysates to protein-depleted rats, with K omitted from the basal ration, that tissue protein synthesis was markedly impaired, but that the addition of KCl reestablished the full nutritive potentiality of the hydrolysate.

There are probably other nutritive essentials also to be considered in parenteral alimentation. For example, we have observed that an absence of phosphate ions also depresses tissue protein synthesis, even with K present in the diet, despite an adequate intake of calories, amino acids and vitamins.

I do not believe blood plasma alone will function adequately in total parenteral alimentation, due again to its low K content, and Dr. Howard showed here, too, that K increased the nutritive value of plasma.

The main purpose of my remarks is to emphasize the point that we can at least fill some of the gaps in our information about the mechanisms determining the utilization of protein hydrolysates or blood plasma while continuing to worry about caloric deficits. Perhaps when intravenous fat emulsions are perfected that worry, too, can be eliminated.

DR. BUTLER: Dr. Howard rightly called attention to the loss of gastrointestinal secretions as a source of K loss and he wondered how much of the K loss was due to something else such as alarm reaction. A patient whom Dr. Lowe will recall may be cited to answer the question. The patient had ulcerative colitis and he was having bloody diarrheal stools of close to a liter a day. He had a hypochloremic alkalosis with low serum K and an EKG indicative of K deficiency. In spite of his dehydration and diarrhea, he was losing as much and more K in his urine than he was in his diarrheal stools, suggesting an alarm reaction that resulted in this abnormal loss of K in the urine in spite of K depletion.

Second, Dr. Cannon seemed to wonder why clinicians were not paying more attention to the parenteral use of amino acids. In spite of the K deficit of amino acid preparations which has now been corrected, the reports of Doctors Howard, J. S. L. Brown and S. Werner, I believe, show that well nourished patients suffering an alarm reaction do not retain much of the administered N. Fortunately, most parenteral fluid therapy is for the previously well nourished acutely ill patient in whom oral feedings can be resumed in 12, 24 or 48 hours. Under such circumstances the addition of amino acids to a continuing intravenous drip introduces a hazard of bacteriemia that counterbalances the possibly slight improvement in N balance. On the other hand, the badly depleted chronically ill patient, who has his homeostatic mechanism set for conservation and repair of tissue, may benefit by retaining the added N, particularly if the parenteral feedings must continue over several days. In such patients amino acids may be an essential part of therapy.

DR. KINSELL: In the early days of the Macy Conference, at the time of the last war, the matter of the possibility of modifying favorably the N imbalance, which resulted as one of the manifestations of the "alarm reaction" was a subject of considerable interest. There has been discussion in that field since then as to whether under any circumstances (short of giving plasma) one can favorably modify or prevent the negative N balance, under these conditions. This is thought by many to be referable to a relative hyperadrenocorticism. I wonder if Dr. Howard has any recent observations on the use of testosterone plus a high level of protein intake, plus K as compared to testosterone, plus protein but without additional K. I would also like to beam a question in Dr. Fenn's direction — the matter of his little men in relation to K outside of cells and within cells. Dr. Butler some years ago reported very low serum K levels during testosterone administration in association with thoroughly normal intracellular concentrations. Under those circumstances, at least the ratio of extracellular to intracellular K was upset. I wonder if Dr. Fenn has any idea how his little men get confused under those circumstances? (J. Lancet 73:163, 1953.)

DR. BUTLER: In the experiments where a very low serum K was encountered during the administration of testosterone, there were not only more positive N and K balances but also very positive water and Na balances. According to calculations based on Darrow's arithmetic of Cl being extracellular, Na and water were going into the cells; so that, in spite of the fact that K was leaving serum to go into cells, cell K concentrations may have been low.

Dealing with hypercalemic states it would, I think be indicated to use amino acid solution without K. You all know of the work in which it was shown that meat was extremely toxic to animals with acute renal insufficiency and I think, therefore in hypercalemia there would be a use for these solutions of amino acids without K.

DR. METCOFF: I wonder if I might comment on a few of the questions that Dr. Howard has raised. Firstly, if I understood his charts correctly it seemed that the amount of K provided in repletion of all except the last

patient amounted roughly to 2 to 3 mM. per kg. of body weight. As Dr. Gamble has pointed out in the Lane lectures this small amount could only provide a small supplement to the 5000 or 6000 mM. of K ordinarily present in the body water. Skin losses, alone, might account for 4 to 5 mM. daily. Secondly, Dr. William Bergstrom has shown in rats that a sizeable proportion of K may be withdrawn rapidly from bone. An amount of K equivalent to that contained in a kilogram of intracellular water in an adult human may be removed in 24 to 48 hours. Both skin losses and a reservoir in bone complicate the proper evaluation of electrolyte balance studies. Finally, Dr. Robert Schwartz, stimulated by an observation of our group and on Dr. William Wallace's suggestion rapidly repleted a series of K-deficient rats. He noted that these animals retained a very large quantity of K in the intracellular phase. At the end of repletion the excess K offered was promptly excreted and as a result, the animals did not get into serious difficulty.

DR. HOWARD: I'm a little sad about this because all those questions I asked haven't been answered and a lot more have been fired that I don't know the answer to. So far as Dr. Zimmerman is concerned, I think I can only say that I agree with everything that he said. I didn't mean to say that nobody went into K depletion without having enteral fluid losses, I just said that we had not happened to see them. And, I agree with what Dr. Cannon said, and thank him for his comments. As far as Dr. Butler's remark about the place of the alarm reaction, I did not mean to say that it played no role, although I must confess that I think the whole business is a little bit overdone as far as this K depletion syndrome in general is concerned. His patient with chronic ulcerative colitis might still be alarmed but his adrenals would have been pretty well worn down, I think, by that time. I don't know why he was putting out a lot of K in his urine.

Several questions came up about the use of amino acids. We have used these as nutritional aids in intravenous feeding and have not felt that there was any undue risk of septicemia involved. In the 1945 case that I described, only glucose and KCl were given, but later we administered the K in glucose and amino acid mixtures.

Relative to Dr. Cannon's observations that feeding of one needed constituent gains greatly enhanced value, if the other needed constituents are simultaneously fed, some years ago our studies showed that gram for gram of N, intravenous amino acids and sugar were just as well utilized as beef steak and potatoes. A group of workers in another city could not confirm these observations, but the difference may have been that our intravenous mixtures included 60 to 90 mEq. of K each day while theirs contained none.

The hour grows late, and I do not believe I can answer with any satisfaction the other questions asked.

DR. GARDNER: There are quite conflicting reports in the literature concerning the effects of digitalis on cardiac muscle K. We became interested in the possible interaction between digitalis and the desoxycorticosterone type of adrenal hormone and carried out some experiments in which we gave rats various combinations of ouabain (strophanthin-G) and desoxycorticosterone acetate (DCA) over a 30-day period. Male albino rats (200 g. weight) were placed on a diet of generous Na and adequate K content. DCA was injected subcutaneously once daily, 5 mg. in aqueous suspension. Ouabain (strophanthin-G) was injected subcutaneously twice daily in aqueous solution. For 30 days the following regimes were instituted: Group A—controls, no therapy; Group B—DCA alone; Group C—DCA plus ouabain 6 mg./kg./day; Group D—DCA plus ouabain 3.4 mg./kg./day. At the end of this time cardiac muscle was analyzed for water, Na, K, Ca and Mg. The data indicated that both dose levels of ouabain largely inhibited the K depleting action of DCA on cardiac muscle in the rat. Ouabain alone appeared to cause diminished Mg concentration in cardiac muscle. These findings suggest that DCA and ouabain are competitive with respect to the K concentration of cardiac muscle in the rat. The unexpected relationship between ouabain alone and cardiac Mg concentration is of interest in light of the known therapeutic effect of Mg in abolishing certain manifestations of digitalis toxicity in man.

Electrocardiographic Changes Related to Disturbances in Potassium Metabolism

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THE electrocardiographic alterations occurring in the presence of hyperkalemia and hypokalemia have been of great clinical value in the recognition and study of the course of such abnormal states. Electrocardiograms gave the first conclusive evidence that some anuric patients died because of excessive amounts of K in their blood plasma.[1] On the other hand, ECG tracings early gave a clue to the marked body depletion of K that sometimes occurred with excessive losses of electrolytes in urine or gastrointestinal secretions.

There is a crude correlation between the level of K in the serum and the ECG picture, which is more valid in the hyperkalemic than in the hypokalemic states. If the level of K in the serum rises simply as a result of the ingestion of a K salt, there is an excellent correlation between the increased voltage of the T waves and the increments in the serum K. However, in clinical states of K intoxication, it cannot be stated at what specific concentrations of serum K the ECG will show a particular phase pattern.

The hypokalemic states would appear to be even more complicated metabolic disorders and the level of serum K cannot be quantitated by the ECG. While the ECG changes in hyperkalemic states in human

beings would appear to be related to an increased extracellular-intracellular ratio of K ion, there is much more uncertainty as to whether, in the hypokalemic state, the ECG abnormality is related to a simple reduction of the ratio of extracellular K to the K in the intramyocardial fibers. The intracellular K in the heart muscle of the turtle remains remarkably constant during perfusion of the heart in the time required for the characteristic ECG changes to appear, with either an excessive amount or the absence of K ion in the perfusate, but whether this is an indication of what occurs in the human heart is unknown.

In general, the first ECG alterations that occur in the presence of progressive hyperkalemia would seem to be related to a disturbance in the depolarization, excitation or conduction processes, whereas, in the hypokalemic state, there seems to be primarily a lag or disturbance in the repolarization phase.

The sequence of ECG changes as the value for K in the serum rises from 4 to 8 mEq. per liter or higher is well known, consisting in sequence of an increasing voltage of the T waves, a slight increase of width of the QRS complex, disappearance of P waves and a marked intraventricular block. The last feature may have a superficial resemblance to what is traditionally known as "right bundle-branch block" (figure 1). The ECG changes are in part dependent

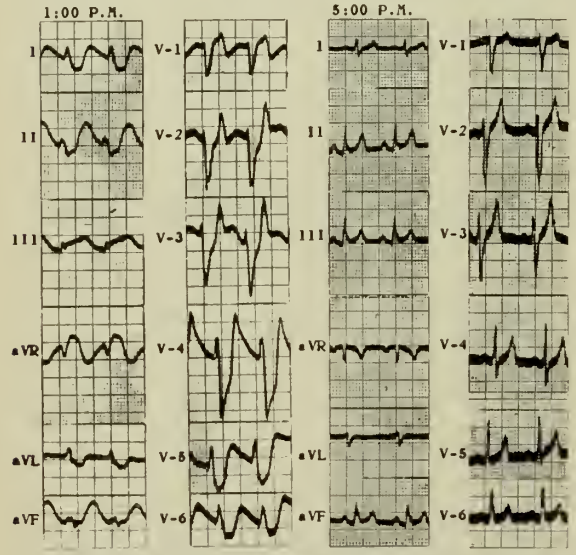

Fig. 1. Electrocardiograms for patient with uremia and paralysis; the serum K at the time of the first record was 9 mEq. per liter. The tracings are characteristic for the late stage of K intoxication. After the infusion of dextrose in isotonic solution of NaCl the electrocardiogram recorded 4 hours later was found to be nearly normal. The sharply peaked T waves were the only suggestion of persistent hyperkalemia. (Case reported by McNaughton and Burchell, J.A.M.A. 145:481-483, 1951.)

on the concomitant concentrations of Na in the serum and may be influenced slightly by the intravenous administration of Ca. When the value for K in the serum is low — 1.5 to 3.0 mEq. per liter — the ECG is characterized by a long Q-T interval with a terminal undulating potential and, usually, by a

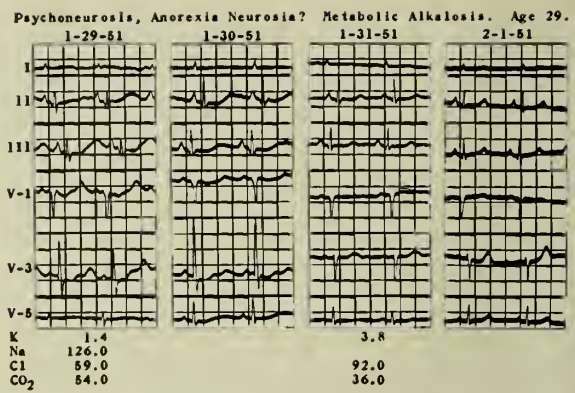

Fig. 2. Electrocardiograms taken on a patient with a severe hypokalemic state which was thought to be related to persistent vomiting. The first and second records show the commonest and most typical form of electrocardiographic abberation with an undulating potential occupying practically the total diastolic period. The accentuation of the P wave, sometimes noted in cases of hypokalemia, may be noted in leads II and III.

depression of the S-T interval; in such records depression of the interval indicates a relative negativity in the electric field facing the epicardial surface of the heart (figure 2). The increased Q-T interval is readily distinguished from that due to hypocalcemia, in which the first part of the S-T interval is flat and the T wave is well formed. We have sometimes preferred to speak of the duration of electric activity rather than of the Q-T interval to avoid the controversy as to whether the prolonged period of recovery of the ECG to an isoelectric line is related to a deformed T or U wave. It is important to note that in hyperkalemic states, a decrease in serum K is attended by restoration of the ECG to normal or to its prepotassium-intoxication pattern, but that in severe, usually chronic, hypokalemic states, the ECG sometimes may not return completely to normal for more than a week, even though the depletion of K seems to have been well managed. Such instances suggest that an organic change might be present in certain cases — similar perhaps to those pathologic lesions that have been reported in rats deficient in K and protein. Up to the time of this report, studies of the hearts of the few patients dying with severe electrolyte disturbances at the Mayo Clinic have not revealed any myocardial lesion which might be ascribed to depletion of K.

Potassium salts frequently have been used in the treatment of cardiac arrhythmias, particularly ventricular extrasystoles, and little evidence of their efficacy has been forthcoming. Noteworthy exceptions are the ventricular arrhythmias related to severe intoxication with digitalis, in which the extrasystoles may be dramatically abolished by the administration of K salt (figure 3).

In view of the place of importance attained by ECG tracings taken from the peripheral electric field of the body, investigations[2] have been carried out in which the potentials have been recorded simultaneously from within the cardiac cavities and the epicardial surfaces under conditions of varying con-

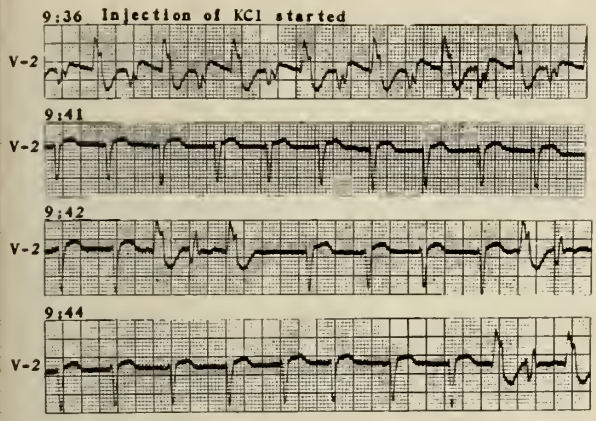

Fig. 3. Electrocardiograms showing wide QRS complexes alternating in polarity and felt to be related to digitalis (digitoxin) intoxication, and the change to normal following intravenous admiinstration (by drip method) of an isotonic solution of NaCl containing 20 mEq. of KCl per 250 cc.

centrations of K in the serum. Isolated hearts of turtles and dogs were studied, because such experiments allowed the most accurate control of the quantity of K in the coronary perfusate, particularly when low values for K were to be studied. Fatal intoxication related to rapid intravenous infusion of K also has been studied in the intact animals, the potentials being recorded from either cavity and the right and left ventricular surfaces.

The major effects of an excess of K on the isolated heart of a turtle were similar to those exerted on the isolated heart of a dog; that is, a prolonged QRS interval with terminal wide monophasic or diphasic complexes. However, in the turtle heart the atria and sinus venosus were more tolerant than the ventricle to an excess of K; both mechanical contraction and electric activity of the atria ceased long after they did in the ventricles. An increase in voltage of the T waves in the epicardial electrocardiograms was observed when the amount of K in the perfusate was increased; the width (duration) of the T wave was not decreased. The ECG changes produced by excessive amounts of K could be partially reversed by the addition of Ca in sufficient amount to restore the original K/Ca ratio in the perfusate (but at a higher concentration of each). Reduction of the Na content in the presence of excess of K enhanced the toxic effects of the latter; an increase in the concentration of Na in the presence of an excess of K partially protected (electrocardiographically) the heart from the effects of the latter. Restoration to normal of an originally low concentration of Na in the perfusate partially reversed the alterations in the ECG produced by an excess of K.

Complete absence of K from the perfusate caused prolongation of the P-R, QRS and S-T intervals in the ECG of the turtle heart. In these records there was early lengthening of the Q-T interval wherein there was no U wave potential to confuse the picture. Except for slight or no widening of the QRS complex before the development of A-V dissociation, similar changes took place in the perfused heart of the dog. These ECG changes in the dog heart were not dissimilar to those ECG abnormalities found in hypokalemic states among human beings.

Although the terminal ECG picture related to either an excess or deficit of K in the perfusate might be labelled "ventricular fibrillation," there was a distinctive difference between the two states. When the amount of K was excessive, the isoelectric periods were longer and the potentials developed slowly, producing a rounded appearance; whereas, when K was absent from the perfusate, the fibrillation characteristically began with many sharp spikes at a frequency of 450 to 500 cycles per minute. If the perfusate was changed back to that containing elec-

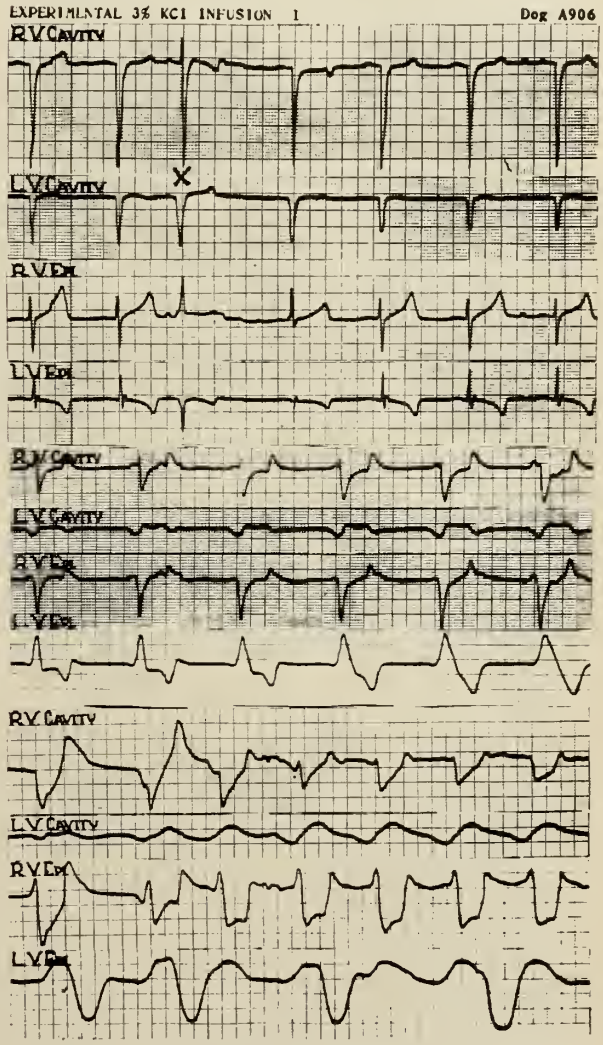

Fig. 4. (*a*) Electrocardiographic records taken early during the rapid intravenous administration (drip method) of a 3 per cent solution of KCl. Regular P waves have disappeared but it is to be noted that when one spontaneously occurs there may be normal A-V conduction (beat, marked X). (*b*) The continuous record showing progressive beat-to-beat change in the configuration of the QRS complexes, yet with the maintenance of general pattern of endocardial-epicardial excitation. (*c*) Record just preceding the terminal undulating potentials of ventricular fibrillation. Of particular interest is the record taken from the left ventricle showing a 2:1 electric effect in the recovery process. R.V. = right ventricle; L.V. = left ventricle; Epi. = epicardium — records made by the unipolar technic; Wilson type of central electrode.

trolytes in normal concentrations, the ECG was rapidly restored to normal in either instance, providing the arrhythmia had been present a short time.

Lithium in concentrations of approximately 25 mEq. per liter was found to counteract many of the ECG effects of an excessive amount of K; for instance, it shortened the delayed intraventricular conduction time and separated the components of electric activity when the terminal type of monophasic or diphasic potentials characteristic of an excess of K was produced. These results seem at variance with the results reported in the literature based on experiments with lithium in the intact animal. The latter feature may readily explain the difference.

When a 3 per cent solution of KCl is given by rapid intravenous drip to the intact dog, ECG changes develop rapidly, and ventricular arrest followed by ventricular fibrillation with large undulating potentials appears, even though the total amount of K injected is less than 300 mEq. (less than 20 mEq. per kg. of body weight). In some instances, with such rapid infusion of large doses, a temporary A-V dissociation has appeared, there being a continued regular atrial activity as shown by direct atrial leads and complete absence of registered potentials within the ventricles or on their surfaces. Simultaneous records of the potentials from within the cavities and from the ventricular surfaces, by means of the unipolar technic, never have shown evidence of any simple bundle-branch block as judged by the traditional criteria for such defects. Characteristically, there appears to be a gross intraventricular block; one unique record showed evidence of a 2:1 intraventricular block affecting a large mass of the left ventricular muscle (figure 4).

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The Relation of Potassium Metabolism to Cardiac Function

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It is now almost commonplace that reports of investigations of the effects of electrolytes on the heart cite the pioneer studies of the professor of medicine at University College in London published about 70 years ago.[5] Thus Sydney Ringer's demonstration that continued function of the isolated frog's heart in a perfusion system involves a nice balance among concentrations of Na, K, and Ca is widely known. Perhaps less well known are certain related historical facts, some amusing, some provocative:

1. His classical contribution[5] was something of an afterthought since an earlier study of the same problem had been invalidated by Ringer's dismaying finding that the saline solution had been prepared with pipe water of the New River Water Company. And this pipe water was not distilled water.

2. A contemporary of Ringer's, James Blake, engaged in a polemic[2] which in effect stated that it is illogical to assume "—that the effects produced by pumping a saline solution through a dead frog's heart can be used to determine the general physiological action of a substance——."

3. Chemical cousins of K and of Ca, namely rubidium and strontium, added to the perfusion fluid were in most particulars indistinguishable substitutes for K and Ca.[6]

It is the latter observation which appears to be especially refreshing in relation to current uncertainties concerning cardiac-K interaction in man. Rubidium does appear to be distributed within the body in depots which parallel K, although in much smaller quantity.[9] In addition Rb has been shown to prevent myocardial lesions which otherwise develop in rats maintained on a diet deficient in K.[3] Granted that the isolated frog heart is not the heart of a patient with K intoxication produced by anuria and that the K-deficient rat is, in a sense, hardly analogous to a postoperative subject sustained on fluids lacking in K, nevertheless the following question may be raised: Are some of the cardiac and other disturbances attributed to derangements of K metabolism conditioned by related changes in the metabolism of Rb and other trace elements? Such conditioning influences would, to be sure, take their place along with more readily measurable and authentic factors such as Ca, Na, and pH.

Preceding authors have already stressed the facts that K deficit or K intoxication may produce striking cardiac disturbances both in intact animals and in man. Impaired cardiac function related to excess or lack of K has also been demonstrated *in vitro* using the isolated heart of frog and terrapin, the heart-lung preparation, and isolated papillary muscle.

Let us turn now to the assessment of alterations in cardiac function associated with aberrations of the metabolism of K at the clinical level in man. The ECG is our principal guide to the demonstration of abnormalities of cardiac function associated with deficiency of, or intoxication with, K in clinical situations. If the ECG deviates from the empirically determined normal in a certain characteristic fashion, a disturbance in cardiac function may be inferred. The degree of certainty of this inference is enhanced by appropriate chemical and clinical information. The question then arises as to whether

the extent of this ECG deviation from the normal correlates precisely with the ability of the heart to discharge its primary function—namely the pumping of blood at a rate adequate to satisfy tissue needs.

An ECG is an end-product of complex and numerous interacting forces which affect the electrical activity of the heart and surrounding tissues. It is, therefore, patent to note that obtaining and reading an ECG is not equivalent to measurement of systemic or pulmonic blood pressures, of cardiac output, or to evaluation of purely clinical evidence bearing upon the balance between blood pumped and tissue requirements. Furthermore, direct studies of cardiac function in man in relation to ECG changes presumably mediated by K as an isolated variable are neither available nor easily done. Nevertheless, the great limitations of using the ECG to predict the functional capacity of the heart even in specific diseases of the organ have been repeatedly emphasized. Thus, the following deductions appear to be justified: First, given a disturbance in K metabolism, minimal ECG evidence of too much or too little K is consistent with actual or impending abnormality of cardiac function. In this instance the ECG end-product of the action of K on the heart may have been masked by certain cancelling influences which, however, did not similarly alter the functional effects. Second, definite or even striking ECG reflection of K effect is consistent with minimal functional disturbance of the heart. Here certain reinforcing factors may have unmasked the ECG changes without correspondingly altering the functional status of the heart. At the same time it must be admitted that assumptions based upon clinical appraisal of K metabolism and chemical measurements of serum K, of K balance, or of tissue K yield similarly imperfect evidence of related change in cardiac function in a given patient.

Clear-cut documentation of the vicissitudes of the ECG in reflecting changes in the metabolism of K is found in a study[7,8] by E. P. Sharpey-Schafer. Fifteen to 20 g. of a mixture of equal parts of KCl and K citrate were given to patients with heart disease or with hypothyroidism. Potassium usually further depressed the T waves in the patient with myocardial infarction (figure 1). It appeared to convert inverted T waves to upright deflections in the patient with hypertensive heart disease (figure 1). Finally, in the presence of hypothyroidism this same dose of K appeared to affect the limb leads of the ECG negligibly (figure 1). These greatly divergent electrocardiographic effects of evidently comparable alterations in the metabolism of K appeared to be determined by the particular type of cardiac background upon which the action of K was superimposed.

We have implied that the ECG is an imperfect mirror of both cardiac function and of the presence of K deficiency or intoxication. But the ECG has been of considerable value in the practical definition of limits of safety for the use of K in correcting

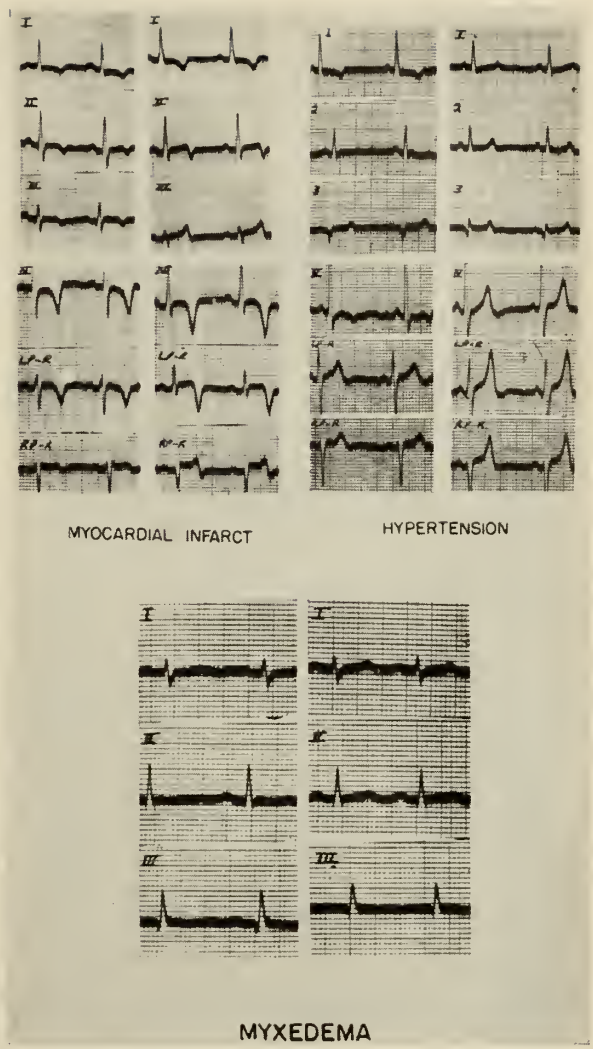

Fig. 1. Above taken from Sharpey-Schafer, E. P., Brit. Heart Jour. 1943, 5.

deficits of the ion. Electrocardiographic disturbances in man consistent with K intoxication may begin to be apparent when serum K has attained a concentration in the range of 6.0 to 7.0 mEq./1.[10] This finding is consistent with the hypothesis that administration of K even in an attempt to remedy a net bodily deficit of the ion is dangerous if, as is often the case, serum K is abnormally high. And, the danger may be just as real whether or not the patient in question has demonstrable ECG changes attributable to the elevated serum K. Although these lines of reasoning are not rigorous, the burden of proof in this matter of safe treatment rests with those who administer K notwithstanding an abnormal elevation of its serum or plasma concentration.

It is our belief that the proper use of K in parenteral therapy is enhanced by study of cardiac function, provided such study is but one facet of the data obtained. Optimal therapy with K requires knowledge of where in the spectrum ranging from depletion to intoxication a given patient's clinical, chem-

ical, and metabolic status occurs. Therefore when the ECG is used in conjunction with knowledge of the patient's underlying disease, renal status, hydration, and the results of chemical analysis of serum, the safety of treatment with K is probably facilitated. On the other hand slavish, isolated use of the ECG as a reliable index of the concentration of plasma K ignores the facts that this index has been shown to be quite rough;[10] that serum K may be elevated without definite electrocardiographic evidence of K intoxication;[4] that K deficiency may obtain without recognizable electrocardiographic correlates.[1]

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DISCUSSION

DR. MUDGE: I would like to ask Dr. Burchell about the reports that one can give more digitalis to patients in severe heart failure if digitalis is supplemented by K. Does he feel that this is a useful and practical form of therapy?

DR. BUTLER: Dr. Gardner didn't provide the information needed. For the record I would like to have one of the cardiologists tell us what they know about the effect of digitalis in different states of K metabolism. Dr. Burchell showed a chart where digitalis toxicity was lessened by the administration of KCl. I have the distinct recollection, as apparently Dr. Mudge has, that K deficiency predisposes to digitalis intoxication and I wonder if that recollection is right or wrong. Dr. Gardner's comments might be misleading.

DR. BURCHELL: Dr. Mudge has brought up the important question as to whether the therapeutic range of a dosage of digitalis might be increased by the concomitant administration of K. I have no evidence to support such a hypothesis. Although I often prescribe a K salt and digitalis to be given together, I cannot remember an instance in which a larger dose of digitalis resulted in a greater therapeutic effect which could be attributed to the K. Certainly it is a field for further careful observations.

Dr. Butler's and Dr. Gardner's remarks have interested me and I also have pondered the relationships that might exist between the effects of digitalis compounds and the adrenal corticosteroids. I have not made any observations which are of sufficient value to mention.

Dr. Earl Wood and Dr. Gordon Moe studied the effect of digitalis on the K content of the isolated heart, working in Dr. Visscher's laboratory, and Dr. Visscher may wish to comment on this study. If I remember correctly, the isolated heart lost K at a faster rate if it was poisoned by digitalis.

DR. TARAIL: I'm afraid it will look as though Dr. Mudge and I are in collusion. The serum K measured in Sharply-Schafer's laboratory underwent comparable increases in each of the patients; as I recall the increases were of the order of 1.5 mEq. per liter.

With respect to the digitalis–K problem I certainly have very little to add to what Dr. Burchell has already stated so well. I would like to call attention, however, to the apparent ameliorating effects of digitalis on the ECG in patients with K intoxication, which Levine and Merrill (Am. Heart J. 43:437, 1952) have recently emphasized. We too had seen evidence of the fact that in digitalized patients K intoxication appears to produce much less in the way of ECG changes than obtains in patients who were not getting digitalis (Am. J. Med. 6:828, 1948). This is an impression that is, of course, difficult to document authentically because we are usually dealing with patients with profound renal insufficiency who are subjected to various forms of therapy and lack of therapy. Furthermore, pericarditis, anemia, hypertension, coronary disease comprise only the beginning of a list of non-K factors which may condition the ECG under these circumstances.

I remember a patient whom we followed in Dr. Peters' department, taking blood serum for K analysis and ECG tracings each morning for 7 days. The patient was anuric and serum K slowly climbed from a level of about 6.4 mEq./l. to 7.6 mEq./l. The electrocardiogram remained unchanged despite this progressive rise in the concentration of serum K. The morning the patient died, however, the T waves, *without change in amplitude,* became peaked. At the same time (serum K had risen to 7.9 mEq./l.) the P waves disappeared and the QRS complex increased in duration, although it remained within the so-called normal limit. Shortly thereafter the patient died. Cogent evidence bearing upon the problem of why more striking ECG changes were not found was not forthcoming. But the fact that this patient had been getting digitalis, as against others with more striking ECG findings, suggested the possibility of a suppressive effect of this drug on the ECG image of K intoxication. It might also be well to reemphasize our belief, perhaps exemplified by the clinical course just described, that death from K intoxication may be just around the corner notwithstanding an innocent-looking ECG.

The Pathology of Potassium Deficiency*†

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Potassium, which is quantitatively the most prominent intracellular cation, is one of the 17 or 18 elements which have been shown to be essential for the integrity of the mammalian organism. Although diets containing insufficient amounts of this element may interfere with the growth and doubtless other physiological processes of rats, certain critical levels (0.17 per cent) must be reached before characteristic morphological changes manifest themselves, in this species at least.[1]

Because of Sidney Ringer's demonstration of the importance of "potash salts" on the frog heart,[2] i. e., reduced concentration in the perfusate leading to delayed relaxation so that there was a tendency to a tonic systolic state when only Na and Ca were present, it was most gratifiyng to find lesions in the myocardium of rats placed on a diet extremely deficient in this element (.01 per cent), yet adequate in other respects.[3] Similar lesions have been described in mice, swine and calves[4] and most recently in dogs.[5] In the growing rat, morphological alterations have been observed as early as the eighth day after the animal has been placed on the deficient diet. First, the cardiac muscle fibers lose their striations and assume a hyaline-like appearance. Next, such fibers disintegrate; the nuclei become pyknotic and leukocytes infiltrate the area. Single fibers or areas of myocardium covering as much as a low-power microscopic field may be involved. In any case such areas are replaced by connective tissue cells and fibers. It is of interest that, in animals which have been fed the K-deficient diet for as long as 327 days, fresh lesions may be observed side by side with older ones; a most intriguing question is why certain fibers succumb before others lying adjacent to them. It should be pointed out that cardiac musculature is not solely susceptible to K deficiency; dietary restriction of two other essential nutrients: thiamine and alpha tocopherol leads to similar lesions in certain mammalian species.[4] No studies on specific biochemical reactions in which K is known to play an important role have been reported on heart muscle. It is likely that such will eventually be demonstrated since evidence for physiological disturbances may be found in ECG tracings in experimental animals and man.[4,6]

In striated muscle, dystrophic lesions, that is necroses of muscle fibers and proliferation of sarcolemma nuclei, have been described in dogs[5] placed on a K-deficient diet but not in rats[3] even though such animals were made to exercise to exhaustion.[7] The dogs[5] just referred to develop a flaccid paralysis doubtless primarily of muscular origin. The exercised rats,[7] when removed from the water tank in which they had been swimming, exhibited peculiar tetanic contractions, probably again of muscular origin. No changes in nonstriated musculature have been described in any species.

Another area where morphological alterations have been found in K-deficient animals is the *kidney*.[3] In the rat, after 6 to 8 days on the deficient diet, neutral fat (sudanophilic) appears in the cytoplasm of the tubular epithelium. The cells become distended with lipoid and then die and are desquamated into the lumens of the tubules which in their lower portions apparently become obstructed so that there is dilatation above. The increase in size of the lumens is further accentuated by flattened, newly regenerated epithelium. The kidneys appear larger than normal after some weeks. Unfortunately no studies of renal function or of urinary composition have as yet been reported except "a diabetes-insipidus-like syndrome" in dogs.[8]

Some interrelationships between K deficiency and other inorganic elements and at least one vitamin may be of interest. Since the two closely related elements, Rb and Cs, can substitute for K in certain physiological processes, each of these elements was added to a K-deficient diet.[9] On the K-deficient-Rb-added diet, cardiac lesions fail to appear; Cs protects the heart to a lesser extent. In the kidney a similar protective effect is produced by Rb and to a lesser extent by Cs. Neither of the two elements particularly prolongs life, however. Since thiamine deficiency leads to myocardial necrosis indistinguishable from that produced by K deprivation, it was thought that the double deficiency might play havoc with the heart. To our surprise nothing happened.[10] In the doubly-deficient rats dystrophic lesions were found in the skeletal musculature. The characteristic renal lesions of K deficiency continued to appear in the presence of thiamine deficiency.

As already pointed out, diets of extremely low K content must be prepared in order to produce morphological lesions in experimental animals. It is quite likely, therefore, that in man, pure K deficiency on a dietary basis must be most uncommon, probably nonexistent. However, since conditioned K deficiency can be studied in animals and is becoming increasingly well recognized in man, morphological changes such as have been described in animals should be looked for with care in human autopsy material. Hypokalemia may be encountered in man as a result of lack of absorption (vomiting,

*We regret that lack of space prohibits reference to many of the significant contributions dealing with this subject.

†Some of the original observations reported herein were supported by a grant from the Rockefeller Foundation.

diarrhea), hormonal disturbance (increased insulin, desoxycorticosterone acetate, ACTH, cortisone, Cushing's syndrome), disordered carbohydrate metabolism, familial periodic paralysis, and renal disease. In such situations the duration of K deficiency (hypokalemia) has usually not been particularly long. Electrocardiographic alterations with cardiac failure were first reported by Loeb's group[11] in cases of Addison's disease too vigorously treated with DCA. Paralysis and damage to striated muscle were also found by the Presbyterian Hospital workers,[11] in dogs to which excessive amounts of DCA had been administered. An autopsy has been reported in which fresh myocardial necroses were attributable to excessive DCA therapy for Addison's disease.[13] Electrocardiographic changes have been described during the hypokalemia associated with familial periodic paralysis[14] and other conditioned K deficiencies already referred to.[6]

In our own autopsy material we have carefully examined the myocardium of individuals dying with hypokalemia and as a result of diseases in which lowered serum K concentrations might be expected to be present. As yet, we have seen no changes directly attributable to disturbance in K content. To be sure that necroses, if present, are the result of myocardial K deficiency one should like to know that tissue concentrations in this element are reduced. It would be valuable, therefore, to have postmortem determinations.

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DISCUSSION

DR. DARROW: I wouldn't be sure that human autopsy material would be suitable for the determinations of K. When we were studying certain things on cats and examining the hearts we found that the cardiac K is extraordinarily variable and can vary over a very short period of time so that if during the patient's dying the serum K rises I would think that the heart might very well fill up with it and I would think that your autopsy material might be perfectly meaningless as to what was going on 2 or 3 days before the patient died. Now I think the analysis of muscles postmortem is in a quite different category for the simple reason that the mass of muscle is such that no other tissue, if it chooses to give up K during the dying process, can really fill up a good deficiency in the muscle. So I think you will have to go on being skeptical but take some of the other clinical evidences of K deficiency when you look at the heart.

The Role of Water and Electrolyte Deficits in Infantile Diarrhea

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The average retentions during recovery in 8 cases of infantile diarrhea were 125 g. of water, 9 mM. of Cl and Na and 10 mM. of K/kg. of final weight. No evidence of retentions of intracellular P was obtained. These retentions presumably represent the immediately replaceable deficits which produce the dehydration, acidosis and shock. They do not include the loss due to consumption of tissues produced by undernutrition.

The water balance and evaporative water losses are subject to no great errors and may be accepted with confidence. Because skin losses were not measured but estimated from the evaporative H_2O loss and assumed sweat concentrations, the balances of Na, Cl and K are subject to experimental errors. The error is unlikely to be great for K but may be considerable for Na and Cl. Since more precise data are unlikely to differ greatly from these estimations, the significance of these retentions will be discussed.

First, the evaporative H_2O losses are so high that 70 cc./kg. per day of sweat was formed when the temperature was about 93° F. Stool volumes were never this high during the period of observation, only reaching about 50 g./kg. per day. Hence, the losses are dependent on a high rate of expenditure of water and electrolytes in sweat and stools at a time when intakes are reduced.

Second, it should be pointed out that infants with diarrhea are likely to suffer from or develop severe undernutrition. Previous studies indicate that undernourished individuals contain low muscle mass, low fat but increased extracellular fluids in relation to

fat free solids. Hence, these patients may be expected to attain high contents of Na and Cl/kg. of body weight during recovery. The amounts retained suggest that replacement of extracellular H_2O and electrolyte requires 60 to 100 ml./kg. of body weight of a fluid resembling interstitial fluid.

Third, the retentions of electrolyte provide a new explanation of the acidosis. Previous studies showed that the acidosis was due to decrease in extracellular Na in relation to Cl. Our studies confirm this finding. From the serum concentrations alone, deficit of Na in excess of Cl was previously considered to be the cause of the acidosis. However, the estimated retentions of Cl and Na are usually equivalent and show that no loss of Na in excess of Cl develops in the body as a whole. The serum findings and the retentions during recovery can only be reconciled if intracellular Na has become high. The loss of 10 mM. of K/kg. of body weight explains the high intracellular Na. From the above, the acidosis of infantile diarrhea is chiefly caused by shifts of Na from extracellular to intracellular fluids in patients suffering from deficits of K, H_2O, Na and Cl.

Fourth, the place of $NaHCO_3$ in treatment of acidosis is altered by these concepts. In many clinics, the calculation of the dose of $NaHCO_3$, which will restore extracellular bicarbonate concentration, has been made and justified by a rapid restoration of bicarbonate when this dose is given. The formula generally used is $NaHCO_3 = (25–CO_2)$ 0.7 wt. If the CO_2 is 5 mEq./liter, this formula indicates 14 mM. of $NaHCO_3$/kg. of body weight. Since the formula indicates an amount of $NaHCO_3$ that is greater than total extracellular bicarbonate, some Na enters the cells. The calculation is based on the false assumption that bicarbonate is equally distributed in total body water. For this reason the actual deficits will be calculated on the known distribution of Na in the body. Using a serum bicarbonate of 5 mEq./liter, the following gives the excess of Na required to restore extracellular bicarbonate:

(25-5) 0.15 = 3mM. of $NaHCO_3$/kg.

$25 \times 0.1 = 2.5$ mM. of $NaHCO_3$/kg.

The first formula calculates the rise in Na necessary to restore bicarbonate in the diminished extracellular volume. The second formula calculates the Na necessary to expand extracellular volume when administered with appropriate amounts of NaCl and water. If more than this amount of $NaHCO_3$ is given, Na must enter the cells or extracellular bicarbonate concentration must become abnormally high. The amount which can enter the cells depends on the magnitude of the deficit of K or Na in the cells and the extent to which the K deficit is already replaced by Na. The retentions indicate that Na is already high but probably not as high as would occur with similar deficits of K and no extracelluar acidosis. Obviously with a particular patient one cannot estimate the probable transfer of Na to the cells and, therefore, one cannot calculate precisely the appropriate dose of bicarbonate. This is recognized by those who do calculate doses of bicarbonate since they recommend only about half of the calculated dose.

In practice, we have found it expedient to replace extracellular fluid by a mixture containing Na and Cl in the proportions found in extracellular fluids and at the same time KCl is made available in amounts which are unlikely to raise serum concentrations to toxic levels and are sufficient to prevent low serum K concentrations.

Replacement of extracellular volume by interstitial fluid actually gives about the same amount of $NaHCO_3$ in relation to NaCl as one half the amount that the formula predicts. However, the rise in extracellular bicarbonate concentration is apparently less rapid. The explanation of this finding must be sought in the relative rates of exchange at the cell membranes. In acidosis the cellular replacement of deficits of K is less than two thirds of an equivalence of Na. This means that administration of KCl will impose a considerable load of acid (Cl) on extracellular fluids as K is restored to the cells. When $NaHCO_3$ alone is given probably some Na enters the cell in exchange chiefly for H but the amount is smaller and less rapid than the amount of K that enters when K is available. Hence, a given dose of $NaHCO_3$ will raise extracellular bicarbonate more rapidly and to a greater extent when K is not available than when K is available. However, this result does not indicate more effective treatment because cell composition becomes more abnormal.

We do not know precisely the harmful effects of deficits of cations in the cells. We do know that injury to the heart, intestinal distension and paralysis may result from K deficiency.

It is possible to estimate the probable role of the deficits of H_2O, Na, Cl and K in the production of certain symptoms of diarrheal dehydration. The weight loss and changes in skin turgor are largely caused by the deficits of H_2O, Na and Cl. Shock with the accompanying reduction in plasma volume, the reduced circulation and the oliguria are likewise caused chiefly by deficits of H_2O and extracellular electrolyte. Initial anorexia and vomiting can also be explained on this basis. However, intestinal distension, late myocardial failure, poor muscle tone and weakness are apparently due to K deficits. Potassium losses play a crucial role in the acidosis. From the above analysis, treatment with H_2O, Na, Cl and blood should prove fairly effective for the initial dehydrated state. Potassium should prove advantageous chiefly in the more effective stabilization of the acid-base equilibrium and the improved intestinal and muscle tone and the improved circulation after extracellular water and electrolyte has been restored. If food with its abundant K can be taken easily, little or no improvement in mortality would be expected, though general vigor during convalescense should be better with KCl. However, if food is not tolerated, replacement of K as well as H_2O, Na and Cl should prevent many of the late complica-

tions — namely weakness, failure of recovery of normal intestinal tone and motility, loss of appetite, weakness and myocardial failure and perhaps sudden collapse. In this connection, it must be kept in mind that parenteral fluid therapy without K produces K deficits in normal individuals and such therapy is particularly dangerous in diarrhea which produces increased losses of K in stools and urine. Hence, large deficits of K occur chiefly in prolonged diarrhea or in patients receiving treatment with NaCl and $NaHCO_3$ at a time when food cannot be taken or is poorly absorbed.

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The Effect of Cation Exchange in Muscle on Acid-Base Equilibrium in Metabolic Alkalosis

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Previous work has shown that, under certain circumstances, a predictable relationship is manifest between the concentration of electrolyte in extracellular fluids and the composition of muscle. The association of metabolic alkalosis with decrease in K and increase in intracellular Na of muscle is well substantiated for experimental animals and patients. The present discussion will present data which will appear soon in the Journal of Clinical Investigation. The data show that restoration of serum bicarbonate in metabolic alkalosis with K deficiency is dependent primarily on the exchange of cations between extracellular fluids and muscle and not on the renal excretion of cations. The data throw light on one aspect of the so-called biological equilibrium between extracellular and intracellular fluids.

Rats were rendered alkalotic and deficient in K by diets low in K and injections of desoxycorticosterone. After discontinuing DCA injections, one group was treated while on a diet low in Na, Cl and K with hypodermoclyses of 6 mM. of NaCl/kg. daily; a second group received 6 mM. of KCl/kg. daily. Six days of injection of 6 mM. of NaCl/kg. failed to alter the abnormal acid-base equilibrium of serum or the abnormal muscle composition. Injections of equivalent amounts of KCl gradually returned the serum and muscle compositions to normal.

The rats receiving NaCl excreted the NaCl essentially quantitatively. The rats receiving KCl excreted a more acid urine (lower pH, higher NH_4 and higher titratable acidity) than the NaCl rats. Furthermore, the urine became more acid than while on the diet before the injections were started. Most of the injected K was retained until about 15 to 18 mm./kg. had been injected. Excretion of K did not approach the amount of K injected until about 20 mM./kg. had been retained. Accompanying the retention of K, about two-thirds of the equivalent amount of Na was excreted despite the absence of Na in the diet.

The paradox of recovery from alkalosis during excretion of an acid urine can be explained by the exchange of cations between extracellular fluids and intracellular fluids of muscle. In this exchange about 3 mEq. of K are exchanged for 2 mEq. of Na. In order to preserve electric neutrality, there must also have been a net exchange of about 1 mM. of K for H. Since the K was administered as KCl, this would be the equivalent of addition of HCl to extracellular fluids and explains displacement of bicarbonate from extracellular fluids. Thus, the reduction of bicarbonate in extracellular fluids was dependent on the exchange at the muscle membrane and the kidneys did not play a role in overcoming the extracellular alkalosis.

One may calculate that the exchange of cations in the muscle when KCl was administered in effect imposed an acid load on extracellular fluids. The load was greater than the total bicarbonate in extracellular fluids; it was approximately equivalent to the excess acid excreted (titrable acidity, plus NH_4) plus the decrease in extracellular bicarbonate plus the change in buffer base of blood.

The data brings out nicely that acid-base equilibrium of plasma cannot be discussed without reference to changes in intracellular composition. For instance, in this type of alkalosis, the excess of Na in relation to Cl in extracellular fluids is considerably less than the deficit of K minus the excess of intracellular Na. In effect the cells are more acidotic than the extracellular fluids are alkalotic. These experiments and other observations on the relation of muscle composition to acid-base equilibrium of serum define certain conditions which must be met in discussion of net ion exchanges at muscle membranes: (1) alkaline pH of serum leads to net loss of muscle K and net gain of intracellular Na; (2) acid pH of serum leads to net gain of muscle K and loss of intracellular Na; (3) increase in serum concentration of K leads to net increase in muscle K and loss of intracellular Na; and (4) low serum K leads to net loss of muscle K and increase in intracellular Na.

The production of alkalosis of extracellular fluids by K deficit and the production of K deficit by alkalosis cannot be explained by the net exchange at the membranes alone. In both cases, the development of the changes in muscle composition involve a net exchange of cations at the muscle which imposes an excess of cations to be excreted by the kidneys. With K deficit, the load is excreted in part as Cl although the total cation load is not more than can be excreted by normal animals. In alkalosis due to Cl deficit, K is excreted at concentrations of K in the serum and in the urine that do not occur when serum bicarbonate and pH are normal. Thus, the present work does not explain the biologic steady state but defines the load imposed by the cellular fluids on extracellular fluids.

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DISCUSSION

DR. BUTLER: Why were the last two slides* different?

DR. DARROW: The difference in the two slides was confined to the direction of the exchanges. During repair of alkalosis one H ion was transferred to extracellular fluids and two K ions went into the cells in exchange for two Na ions. This accounts for the formation of H_2O and CO_2 in extracellular fluids from HCO_3. In the development of alkalosis, one H enters the cells in exchange for one K while two K ions leave the cells in exchange for two Na ions which enter the cells. This explains the formation of HCO_3 from CO_2 and water.

DR. CANNON: You brought out in the use of the word "exchange" a question which I wish you would help to clarify. In the "exchange" of Na and K, the question which has puzzled me and possibly others is the use of the terms "displace" and "replace" in relation to this problem of Na and K interaction. These terms have been used by others. In one of your balance charts demonstrating an increasing retention of Na, there was no increase in excretion of K. One might expect this to follow if there was a "displacement" of K by Na. How do you relate the term "exchange" to the terms "displace" and "replace" as the latter are often used?

Some talk about "displacement" and some about "replacement." It is a confusing terminology. — I'm afraid I'm not a good enough physical chemist to give you the thing as it is. I think of them all as dancing around as Dr. Fenn pictured them (and I expect "hugging" these phosphate ions) and that the K ions are handsomer and the Na ions do not have anyone to dance with. But, if one of them gets out, Na can get in there and I would think, if you want to speak of the exchange, I am intrigued by the Conway modification of the Donan equilibrium and in that sort of a thing you can set it down on paper and make a nice little story about it that can explain this mechanism. The only thing that you have to do to make Dr. Peters rise in his seat is to say that the Na doesn't behave that way. There is a little pump there (and he doesn't like pumps), but I think all it amounts to is that there is some sort of a factor we have no notion of. You can explain K movements quite well on the assumption that the anions within the cells cannot get out of the cells, that is the large group of organic phosphate compounds and that for some reason or other K is preferably combined with them rather than with Na. Now whether or not the Na is pumped out, it obviously can get into the cells very rapidly and so can K. I mean labeled Na and K indicates they can both go through the cell membranes extremely rapidly; so, whatever is controlling it is not permeability, at least it is not in the muscle. The red cells are a little different; the ions are a little slower in getting through the membranes.

DR. LOWE: Some pediatrcian probably has to support Dr. Darrow. As a person who has been most interested in what Dr. Darrow has tried to teach, I have found that the measurement of the CO_2 and the Cl in the serum of patients, as he and Dr. Howard suggested last evening, is probably the most useful single indication of the degree of K deficit in patients. However, using this measurement, particularly in the last year, we have come upon certain patients, in whom this is apparently not a reliable index, and I hope Dr. Darrow will offer an answer to the difficulties presented by this type of patient. These are patients in whom the CO_2 and Cl concentrations in the serum approach those values expected in K deficiency; in other words the CO_2 may be 35 mEq./liter and the Cl perhaps 85. But, when pH is measured in the serum, it is found to be between 7.1 and 7.2. These are well hydrated patients and it is our impression that they have primary CO_2 retention. These chemical findings occur among infants who come to the hospital in an apparent shock-like condition and during the period of recovery of from 3 to 4 days, persist in having irregular respirations. Now these patients present a considerable clinical problem since the CO_2 and Cl values do not return to normal levels following K therapy. I would, therefore, like to suggest that before we accept the term alkalosis for all patients with a high CO_2 and low Cl in the plasma, the pH be measured. I think this is particularly applicable to infants and perhaps less so to older children and adults.

I would like to support Dr. Darrow in his suggestion of treating acidosis with K-containing solutions. During the past year we have had two patients with severe diabetes; CO_2 in one case was 6 mEq./liter and the other 8 mEq./liter. These moribund children were not treated with bicarbonate solutions, but were rather with a balanced type of polyionic solution containing K among other ions. Obviously they were also treated with insulin and glucose, but the impressive feature was that their CO_2 returned to normal within 18 hours. Furthermore, we did not observe an overswing into alkalosis. It was our impression that their clinical recovery was as dramatic as might have been expected if bicarbonate alone had been used in therapy, but, more important, there was no postacidotic alkalosis. I hope to avoid any argument concerning the pros and cons of alkali therapy in diabetic acidosis, as this was so well discussed by Dr. Guest yesterday. Rather, I want to suggest that dramatic results in terms of restoring CO_2 concentration can be achieved without the use of such alkali solutions.

Dr. Darrow has indicated the explanation for the observed fact that patients with hypokalemic alkalosis can have acid urine. The fact that this may occur was first brought to my attention this summer by Dr. Smith of the University of Minnesota and recently we have had occasion to observe this upon a number of patients who were treated with K. This has been particularly noted

*Slides thrown on the screen during presentation of the preceding paper. We believe the text will be self-explanatory.

in patients with pyloric stenosis who had considerably more acid urine after the first or second day of therapy with K-containing solutions in spite of the fact that their CO_2 was still elevated and their Cl was still depressed. Our first explanation was ketosis; however, it was impossible to demonstrate acetone in their urine and I think Dr. Darrow's charts offer us an explanation for this clinical observation.

DR. HANSEN: There is one compensating feature in regard to hot weather, at least in certain parts of Texas—the drinking water is one fourth to one third isotonic, hence, if one consumes very much in the way of water, some of the deficient electrolyte constituents have been supplied. This may be nature's preventive method. From the practical viewpoint, we have conducted a study in San Antonio where death rates are very high in infants. During a 3½ month period, we had 181 patients who were carried through on Darrow's regime and there were only 6 deaths. After our research team had departed, within a period of 45 days there were 17 deaths out of a much smaller number of patients. Despite the controversy concerning exchange of K in and out of cells, the use of replenishment fluids containing K was associated with a great reduction in the death rate in infants suffering from severe diarrhea. The problem of deaths from diarrhea is a real one in Texas. The latest complete figures for the death rate in infants in the United States (1948) indicated that 25 per cent of the total deaths from diarrhea, enteritis, and dysentery in the first two years of life in the United States occurred in that state. We have less than 5 per cent of the total population of the country, so the problem is a real one.

DR. DARROW: It is interesting how this native Minnesotan caught the Texas spirit and everything is bigger and better for a naturalized as well as native Texan. I don't know that all the native sons of Texas would think he selected the most suitable aspect of the big things in Texas for comment. As to Dr. Lowe's comments, they are extremely pertinent. I think I am partly responsible for the confusion. If you recall, I wrote a paper in which I said there was a relationship between bicarbonate concentrations of the serum and the muscle water. Those data were based on studies of metabolic acidosis and alkalosis in which the animals were permitted to adjust to a deficit of one of the ions—Na, K or Cl. The data were based on experiments on rats which are unsuitable for pH measurements. While we made a few measurements of serum pH, we never thought they represented the pH before withdrawing the blood. For this reason the correlations were calculated with serum bicarbonate concentrations which are not subject to rapid modification during handling the animals. We know now that the correlations of muscle composition with extracellular pH would be as good in metabolic acidosis and alkalosis as with serum bicarbonate concentration.

Recently the muscle composition of rats subjected to respiratory acidosis has been determined. As the bicarbonate concentration in serum rises in compensated respiratory acidosis, muscle composition does not change significantly. These data will be published in the Journal of Clinical Investigation within two to three months. They provide the answer to Lowe's question. The diagram cannot be applied to patients without realizing that many exceptions will be encountered. The fundamental relationship is with serum pH. Perhaps it would be even better if we knew the delta pH across the cell membranes. Doctors Schwartz and Relman had some studies and I saw their data, which demonstrated as profound K deficiency as I think I have seen anywhere and yet no evidence of disturbance in the acid base equilibrium was found. The relation of the composition of muscle to extracellular fluid cannot be an obligatory relationship like a chemical equilibrium. We have always produced K deficiency with alkalosis by giving an excess of Na over Cl. This seems like loading the dice in favor of the result, yet when you consider the experiments which we reported here, the tendency of K deficiency to develop alkalosis is real. This conclusion is supported by the observation that administration of NaCl did not overcome the alkalosis although from the point of view of the extracellular fluids, NaCl is an acid solution. I don't believe there is any doubt that the essential facts as we presented them are correct, but I think you should all be aware and on your toes, as was Dr. Lowe. His observation again emphasizes that one cannot define acid base equilibrium by bicarbonate alone. You have to have the pH and then you have to look at your patients and see what their respirations are doing and make more than a simple diagnosis in terms of bicarbonate and Cl concentration.

Exchanges of Sodium and Potassium in Muscle

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During the lifetime of a living organism, the constituent cellular units maintain an ionic composition that is highly characteristic even in the face of differing ionic environments. Thus muscle fibers, from insects to man, typically have high intra-fibral K and low Na, while the body fluid compositions vary all the way from very high Na to very high K. Clearly some important regulation exists in cells.

This regulation must be a dynamic affair since many studies have shown that during activity the ionic gradients tend to disappear. Likewise, many studies with isotopic tracers have demonstrated that the resting state of a living cell is not the result of a "closed door" policy on the part of the vital unit but rather is due to an active process of redistribution.

Attention is focussed here on the Na and K distribution of the frog sartorius muscle. This is for several reasons, the main one being that Na and K ratios are hardest to explain. Such alkaline earth metals as Ca and Mg in all probability are not free as ions inside living cells but exist in the bound state. There is much indirect evidence to support this conclusion. Chloride and other diffusible anions appear to be distributed simply according to their electrochemical gradients, the usual Donnan ratios being found. Sodium and K, on the other hand, are not bound to any great extent, they diffuse freely across cell boundaries and yet their distribution ratios are widely different from each other.

The normal high-K, low-Na condition found in cells seems to reflect a "physiological impermeability" to Na in the sense that the physiological units do not allow Na to exist internally in concentrations as high as those outside. The nature of this physiological impermeability to Na hence becomes of great interest since it is the factor that determines the balance between inside and outside of the cell for both Na and K. Potassium accumulation seems to be a function of the physiological impermeability to Na, or, stated differently, of the ability of cells to extrude Na.

Evidence is accumulating that an outwardly directed extrusion of Na is the major factor leading to the high K concentrations found in most animal cells. If the outward Na movement is stopped, no K accumulation of any magnitude takes place.[1,2] The kinetics of the Na transport system has been studied, using as a material isolated frog sartorii that have been depleted of K and enriched in Na. With such muscles, rapid extrusion of Na takes place with consequent accumulation of K when placed in normal Ringer's fluid. The rate of outward Na transport is at least 40 mM./kg. fibers/hour, the process having a half time of about 30 minutes. In terms of energy expenditure this transport represents about 80 calories/kg./hour or about half of the normal resting metabolic rate.

The extrusion rate of Na is quite comparable to the total isotope exchange rate noted by other workers, hence no special mechanism for exchange, as distinguished from transport, need be postulated.

The temperature coefficient (Q_{10}) of Na transport is between 3 and 4 as measured from 2° C. to 22° C. The rate is also controlled by both the internal Na concentration and the external K concentration. There is no indication that external Na concentration has much influence on the rate of outward transport of Na.

All of the data are consistent with the idea that living cells, especially at their outer surfaces, possess a chemical constituent capable of binding Na in small amount in preference to K. Presumably this substance must be formed by the metabolic processes of the cell and must be removed or destroyed during the transport of Na. The Na complex must, of course, be capable of moving through the external layers of the cell either as a whole unit or as a part.

A Na extrusion mechanism such as that described here is of obvious importance in relation to excitability phenomena. Since it is highly temperature sensitive and also influenced by a variety of metabolic poisons it may be suggested that many of the pathological redistributions of Na and K are really reflecting a prior breakdown of the Na transport mechanism.

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DISCUSSION

DR. FENN: First I should like to make a very general comment. When I was first interested in K we had trouble getting clinicians to take an interest in the K problems. Now the shoe is on the other foot and physiologists and biochemists are unable to supply the background information which is needed to explain the very complicated results which are coming out of the clinics. I think this is a challenge to physiologists to provide a better framework for clinical use. Dr. Steinbach is one of the few who are working on the basic aspects of this subject. One of the points that I think needs clarification is the relation between the operation of the Na pump bringing K in and the effect of pH or the exchange of H with K. These are at least two of the processes that regulate the K inside, and we don't have a very good idea of how they interlock. Some of the data which Dr. Steinbach presented helps to some extent. I should like to ask him whether he has studied

the effect of pH on the operations of his Na pump. If Na is pumped out in exchange for H^+, then an increase in H^+ outside the cell should bring Na out. But K is also supposed to come out in exchange for H. On the other hand, if Na is pumped out always in exchange for K, then the Na pump should work better into an alkaline solution because this favors the entrance of K. Ussing found that the Na pump is favored by alkalinity inside the frog skin but it was independent of the pH of the outside solution.

DR. MELCHIOR: Speaking as a chemist, I want to talk about the assumptions which are involved in the interpertation of these results. There are many assumptions, stated and unstated. And I think, as a chemist, that these assumptions are all open to question.

My interest in this symposium is due to an interest in complex ion formation; and there are several things which bear on this problem which have been learned from studies of complex ions. For example, *both* Na and K ions form complexes with important metabolites. The exchange of K for Na and H ions reported by Dr. Darrow could very well be explained on some such basis. I do not say that this is the explanation. In fact, the observations could equally well be explained by changes in cell metabolism caused by small changes in the K concentrations – as far as K concentration is concerned, this is exactly what happens. I noticed in Dr. Steinbach's data on the effect of the internal Na concentration on the rate of K uptake by depleted cells that the sharp reduction in rate at low Na was represented by only one point, while data indicating an equally sharp reduction in rate at low external K ion concentrations show several points below the plateau. These data would be equally well interpreted by the opposite explanation, that is, by a metabolic or "active" uptake of K and a forced exit of Na ions. I think we will have to keep an open mind until we find out what substances actually form the kind of complexes which are probably involved.

I want to emphasize that a mechanism for "K pumping" in which the metabolite which complexes K is formed near the membrane of the cell and destroyed near the center of the cell in the course of normal metabolism will account for the uptake of K just as well as an explanation involving a "Na pump." And I repeat that we have no positive evidence as to the type of "pump" which is functioning in this case.

There is one further question concerning the experiment which furnished the single point indicating that low internal Na (high internal choline) caused a reduction in the rate of uptake of K. I wonder if the control in which choline was present outside the cell for 30 minutes is equivalent to exposure to choline for 24 hours.

DR. MUDGE: The evidence which Dr. Fenn and Dr. Steinbach have presented supports the concept of a Na pump for the tissues which have been studied. By very similar reasoning, we have concluded from data from the kidney, that we are primarily dealing with a K pump. There are no *a priori* reasons why different tissues should not have different mechanisms.

I would like to mention one word of caution about experiments in which various compounds are substituted for NaCl in the incubation medium. Before assuming that we are just replacing one inert compound by another, we must have good evidence that the absence of Na and or the presence of the new compound do not have an effect on other phases of tissue metabolism. Whenever we have tried to study a low Na system, there has invariably been a moderate depression of respiration. Besides cation exchange other cell functions can be greatly altered. If lithium is substituted for Na, K uptake by kidney slices is inhibited, but also, as Taggart has shown, the accumulation of p-amino hippurate is depressed. Since cation exchange is not involved in the latter reaction, it is apparent that other pharmacological effects of Li must be considered.

Dr. Steinbach also mentioned the evidence indicating that the gradient of K across nerve or muscle membranes is the major factor, rather than the absolute concentration of K within the cell. However, in other types of cells the actual intracellular concentration of K may be the major determinant for metabolic functions. This morning, Dr. Teng presented some data on this point in relation to glycogen synthesis. In his studies on p-amino hippurate accumulation by kidney slices, Taggart has some very clearcut experiments showing that this cell function is K dependent; again in this instance, it is the actual intracellular K concentration rather than the gradient across the cell membrane which is of major importance. Possibly, these experiments emphasize basic differences in the effects of K on the neuromuscular system and on glandular or secretory tissues.

DR. WILDE: I have followed Dr. Darrow's work for some 10 years, watching for a possible explanation of the relation between lowered plasma K and elevated plasma bicarbonate. I feel he is now well along toward a solution and I am greatly pleased with the result.

The thing of interest here with reference to Dr. Steinbach's paper is the question of the time relation of the Na and K movements in the K deficient rat. Conway and Hingerty (Biochem. J. 40:561, 1946) showed that after you have a K deficiency of dietary origin developed and then begin to reverse by feeding K, that the K goes into the muscle tissue much more quickly than the Na comes out. This to me offers difficulties in terms of a Na pump – the timing is different, the K rushes in but the Na comes out slowly. That by the way is borne out in some of the $NaHCO_3$ observations that Dr. Howard mentioned yesterday. The puzzle is that if one is to promulgate a Na pump the Na should come out of the cells either before or as the K goes in. Also Dr. Darrow has indicated that there is a discrepancy in the *amount* of Na and K transferred. The Na changes occur over a matter of 3 to 6 days. The question is: Does Dr. Steinbach feel that a Na pump should be invoked in this situation and if so how does he explain the different rates and amounts of Na and K movement in K-deficient animals?

By the way, as to whether to call this "exchange," I do not think we should call it exchange until we prove that it really is exchange, as of a K ion for a Na or H ion.

In handling Na data taken from these K-deficient animals, I think we might learn something from Dr. Cannon's observations and others who have made histologic studies. There is an infiltration of connective tissue into muscle as the deficiency is developing. Now this seems to be rather spotty. But recall that connective tissue in general is rich in Na (Manery and coworkers: J. Biol. Chem. 124:359, 1938). – Does newly infiltrated connective tissue bear the increment of Na found? Does anyone wish to comment upon this? I have the impression that the connective tissue changes, the pathological and histological changes, are probably slower than these chemical and Na changes that we are discussing.

Finally recall that there are pharmacodynamic changes during K deficiency: general muscular weakness and changes in the ECG. It is my impression that after K therapy these weaknesses are restored almost at once and before the Na is pumped out of the muscle.

DR. STEINBACH: Dr. Fenn, I am afraid I have no data to answer the question of what the role of intracellular H ion concentration is in muscles. As to the effect of external pH on the Na-extrusion system, within a range of pH 6.8 to almost 8 there is very little effect. I haven't the calculations at hand but the intensity of metabolism is such that I doubt if the production of H ions has more than an accessory role in this sort of an exchange.

In so far as Dr. Melchior was talking as a chemist I agree with him thoroughly.

I believe there is a specific question about choline effects. One of the controls[2] was a half and half mixture of NaCl and choline Cl for the full 24 hours of extraction. In that condition there was a partial loss of K and gain of Na. The recovery was perfectly normal so from that I would say there was no toxic effect of external or internal choline even applied over the whole period of extraction and recovery.

With respect to Dr. Mudge's comment, on the basis of published data on both kidney and brain I cannot see anything which cannot be explained at least as well by a Na extrusion mechanism as by an active K uptake. I did not use Li as a substitute because Li according to its physical, chemical parameters is so close to Na.

I would remind you of Dr. Fenn's comments again, on the association between glycolysis or glycogenesis and the uptake of K. There are two ways of regarding the parallelism; either the K is influencing carbohydrate metabolism or it is influencing K uptake. Judging from Dr. Fenn's older work on liver, the uptake of K seems to be an uptake of an isotonic KCl solution associated with proportionate amounts of glycogen formed. I think I am quoting that paper correctly but from that I would infer that as the glycogen is formed the K just soaks in according to the usual system. Dr. Wilde mentioned the paper of Conway and Hingerty on the recovery of rats from a K-deficient diet. I find it very difficult to believe that these animals were normal because data of other workers on stimulation and exercise of muscle intact in the animal shows a depletion of the muscle of K and a gain of Na. During rest (recovery) the Na goes out of the fibers and K comes back in a comparatively short time.

DR. GARDNER: In reply to Dr. Steinbach's query to Dr. Wilde concerning the delayed Na extrusion in K deficiency treated with K, I would like to support Dr. Wilde. Dr. Wilde, however, quoted the wrong Irishman; it was Conway and Hingerty who made the study.* These workers depleted rats of K by a low K diet. They repleted them with K, sacrificing groups at varying times after the K was given. Skeletal muscle was analyzed for Na and K. Their data are quite convincing that there is a delay in the extrusion of intracellular Na after repletion with K. In some balance studies with K-deficient rats, we noted what may have been the same phenomenon. When K was injected there was a wave of urinary Na which came on the fourth day after the single injection of K.†

DR. DARROW: There is a phenomenon concerning osmotic pressure which must be related to these observations. Despite a constant serum Na concentration, the water per unit of fat-free solids remains essentially the same in rats with K deficiency. The findings indicate that the concentration of Na + K in cell water is considerably less than in normal rats. One must conclude that the osmotic pressure of other constituents or Na + K is different in two groups. The exact mechanism is not understood but may involve changes in the aggregation of anions. Whatever the changes, the restoration of osmotic properties may not exactly coincide with recovery of K. In other words, the release of Na from the cells may occur only when osmotic properties return to normal.

I am skeptical about the relation of the exchange of K for intracellular Na revealed by balance data. I believe actual measurements by muscle analysis are necessary. Conway and Hingerty published data showing a delay in the release of intracellular Na as K was administered to K-deficient rats. Their data are based on muscle analyses. Our data do not bring out this phenomenon. I thought Wallace found the same delay in release of Na as did Conway and Hingerty. Probably Metcoff recalls these data correctly.

DR. METCOFF: I think that that statement appeared in an abstract relating to the repair of diarrhea. As I recall, the point that Dr. Wallace and I were trying to make was that there was a relative ceiling to the rate and quantity of uptake of K. It was very difficult to evaluate the exchange of Na for K, except on the basis of external balance. It was quite true that the loss of Na was slower than the uptake of K. In the replacement experiments in rats done by Dr. Robert Schwartz, which I mentioned yesterday, he showed a very rapid uptake of K to a ceiling or a limit which seemed to be adequate to replace the deficit in one intracellular phase of muscle and then a prompt dumping of the excess. As I recall, a substantial quantity of excess Na remained intracellularly. Now whether one could interpret this as favoring a primary exchange of K and a secondary inadequate extrusion of Na, I do not know. One wonders whether it would be possible to say that there may be a primary changing affinity of the substrate for H ion or a changing affinity of H ion for the substrate with an indifferent exchange of Na and K depending upon the various chemical or electrical gradients in effect at that time.

DR. GUEST: At the risk of seeming to belabor a point, I should like again to cite the studies of transfer of K, P and glucose in red blood cells. Recalling Dr. Fenn's amusing cartoon representing the "Na pump," I like to think of his little K men riding piggyback on molecules of phosphate. I mentioned yesterday the work of Hastings' group showing that the K gradient between plasma and blood cells is maintained by enzymatic reactions of phosphorylation in the glycolytic cycle. With glycolysis in normal blood, studied *in vitro,* when the glucose is used up, there is rapid escape of K and P from the cells; if glucose is then added and glycolysis begins again, both K and P will re-enter the cells, if optimal conditions of pH are maintained.

DR. STEINBACH: I am caught in the trap of my own simplifications here and it would take long to justify some of them. The plain fact of the matter is that I have not, nor have anyone else, figured out what the specific time course of the change is when you go from one steady state to another steady state. For example, in the cases that I reported on, the K-depleted and Na-enriched muscles started at a fixed level. You now change the ionic gradients and you change the whole

*CONWAY, E. J. and HINGERTY, E. A.: Biochem. J. 42:372, 1948.

†GARDNER, L. I., MACLACHLAN, E. A., TERRY, M. L., MCARTHUR, J. W. and BUTLER, A. M.: Fed. Proc. 8:201, 1949.

picture including chemical gradients and presumably some of the electrical factors. What the time course of attainment of the new steady state is I wouldn't want to predict at the moment.

Also, remember the assumption that I made, not directly but implicitly, that the base binding capacity of the cells remained the same. Now, if during K repletion after depletion new anions appeared within the cells, there might be a very rapid uptake of K before there would be any Na extrusion. I have some of my own data, not on humans or on frogs but on worm muscles that show precisely this increase in anion concentration. During treatment with excess K there is new anion created associated with K-uptake. I think that is the point you are mentioning, Dr. Darrow.

About the Conway and Hingerty papers, I have little to add. I still would like to repeat the experiments. Possibly during the drastic dietary changes and the long time involved, new base-binding groups appear so that, in effect, the muscle fibers grow. If so, excess K would enter the cells if the muscle membrane is more permeable to K than to Na.

In respect to the red blood cells and phosphorylation I think the comments made previously apply. I don't know which was first, the chicken or the egg, in that case.

Potassium and Myometrial Function

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The experiments reported here* suggest that the effect of the ovarian hormones estrogen (E) and progesterone (P) on the smooth muscle of the uterus is accomplished by alteration of the K balance of the myometrial cell.

The experiments were performed on 93 rabbits. The maximum tension and the duration of a single isometric contraction cycle were found to depend upon the frequency of stimulation, upon temperature, and upon the K:Na ratio of the Krebs solution in which the muscle was suspended. The technique of Hajdu and Szent-Györgyi,[4] in studying the Bowditch staircase phenomenon was consulted.

We observed that the uterus of the estrogen-treated castrate (EU) exhibited the Bowditch phenomenon, its staircase being similar to that of the frog heart. If electrically stimulated at frequencies within physiological limits (1 stimulus/½–8 minutes) it exhibited a decrease in tension with decreasing frequency of electrical stimulation.

On the contrary the uterus of the estrogen plus progesterone treated castrate (PU) animal shows a Bowditch phenomenon of opposite slope, which was designated "negative staircase" (S− in contrast to S+). This muscle exhibited an increase in tension with decreasing frequency of stimulation.

The uterus of the castrate showed no staircase and was insensitive to frequency changes, a fact which indicated that the staircase was not strictly a property of the myometrium but rather an expression of the dominant hormone effect.

These findings held for the uterus of the hormone-treated castrate as well as for the uterus under natural domination of E (estrus) or P (pregnancy).

One would expect to see slopes intermediate between the extreme S+ and S− if the two hormones are simultaneously administered in various proportions. Experiments have shown this to be true. The staircase was found to be most negative in early pregnancy (which condition can be imitated only if for at least 3 days P is administered without E) suggesting that in this condition E is not present in the living animal. By the administration of E during early pregnancy we expected to produce a leveling effect on the negative slope of the staircase and also a disturbance of pregnancy. Experiments have shown that a single dose of 5 μg. E/4 kg. body weight, administered between the second and fifth day of pregnancy, significantly reduces the slope of the S− and completely interrupts pregnancy. Since the staircase so accurately reveals the delicate balance of the ovarian hormones it is important to understand its nature.

We first believed that the unique behavior of PU (i. e., decrease in tension with increasing frequency of stimulation) is due to incomplete resynthesis of its high energy phosphate. We observed that the ATP/ADP ratio of EU is 2.33, whereas that of PU is 0.79. This assumption can not be completely disregarded in view of the active Na transport which may overlast the contraction cycle and must use a considerable amount of energy,[7] but its significance was somewhat weakened by the observations of Hajdu and Szent-Györgyi[4] with respect to the staircase phenomenon of the frog heart.

They have shown that the steep slope of the staircase present in regular Ringer-Conway solution can be completely abolished if the K concentration of the perfusion fluid is decreased to one eighth the usual level. Fenn[2] and Fenn and Cobb,[3] found that contraction entails a loss of K, they assumed that the resting frog heart contains more K within the cells (Ki) than is optimal for the development of maximum tension and therefore the heart must be stimulated with high frequency to extrude the super-

*The studies were made in collaboration with Dr. G. W. Corner, Dr. J. Menkes, Dr. B. Böving, and Dr. B. Horvath. Stimulating discussions with Dr. A. Szent-Györgyi, Dr. S. R. M. Reynolds, Dr. B. Steinbach, and Mr. M. Goodall are acknowledged.

optimal amount of K and keep it out. If stimulation is discontinued the staircase reoccurs. This effect can be abolished by decreasing the external K (Ko), the increasing gradient being unfavorable for the return of K. They also demonstrated that the staircase disappears at 0° C. whereas its slope steepens with increasing temperature. Serum, desoxycorticosterone, and digitalis glycosides have the same effect as the decrease of Ko. They believe that these substances inhibit the return of K to the cell.

Assuming that the K:Na within the cell (K:Na*i*) is a function of the K:Na outside it (K:Na*o*) we studied the staircase in a series of Krebs solutions in which the ratio K:Na*o* was varied. The effect of the change of the K:Na*o* on the muscle appeared in about 120 to 240 seconds. The rate of diffusion of K being in the order of 1 μ/second, the K*o* can in that time reach a distance of 120 to 240 μ from each side of the muscle, which is exactly half the thickness of our myometrial samples. Whereas with respect to change in temperature EU behaved in a similar fashion to that of the frog heart, the results were somewhat less congruent if the K:Na*o* was varied. In agreement with the behavior of the frog heart, EU exhibited an increase in tension in a few minutes if the K:Na*o* was decreased. The staircase did not disappear, however; its slope was only slightly reduced. If the tissue was first subjected to repeated washing in K-free Krebs during a period of ½ to 2 hours, the staircase disappeared, a gradual decrease in tension being observed after each washing. If the EU was kept in K-free Krebs at 37.5° C. as before and the perfusion fluid was then changed to normal Krebs, the K:Na*o* thus being increased, and if the muscle was stimulated once every half minute, the tension dropped and remained at a low level for about 20 minutes, increasing slowly thereafter. If during this short period of time the staircase of EU was observed a negative slope was seen. This is strictly a transitory effect, however, for after the 20 minute period the staircase was positive again.

The similar effects of temperature and K:Na*o* were more easily observed, and were in good correlation in experiments with PU, increase in each resulting in gradual disappearance of S—.

A striking difference in the behavior of EU and PU with respect to maximum tension also appeared if the K:Na*o* was gradually increased. This treatment also showed that the EU had the greatest tension in a Krebs solution in which the K is reduced by one-half, whereas PU reached the greatest tension in a Krebs solution in which the K concentration was increased three times.

We also observed that the duration of a single isometric contraction cycle increased with decreasing temperature (and with decreasing K:Na*o* in the case of EU), the temperature dependence of the EU being much greater than that of PU.

It may be concluded that estrogen and progesterone alter myometrial function in opposite directions as revealed by measurements of the maximum isometric tension. Their effect can be counteracted or even reversed by change in temperature or in the K:Na*o*. Determinations of the K:Na*i* *in vivo* and also *in vitro* (after alterations in the K:Na*o*) are under way in our laboratory to see whether a different ratio already exists *in vivo* in the contrasting hormonal states, or develops *in vitro* under the experimental conditions. Difficulties in determining the extracellular space of the uterus delay the presentation of these results. The experiments thus far indicate that the K:Na balance is altered in opposite directions by the two ovarian hormones, but whether the absolute quantities or the dynamics of the ionic movement are changed must be worked out. The observed effects on the K:Na balance may not represent the whole effect of the ovarian hormones and may not be generally valid throughout the whole reproductive tract. The general trend of the experiments reported is promising, however.

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DISCUSSION

DR. STEINBACH: In this report the main charm for me is, taking an old physiological phenomenon and making something of physiological significance out of it. The staircase phenomenon has been known for a long time and I think this is a very good attempt to make a use of it. There is in recent literature a fairly comprehensive theory of muscle contraction which says in effect that the ionic gradient is the controlling factor for the tension developed. That is roughly to be inferred from your presentation, I believe, Dr. Csapo. To get direct evidence with respect to this ion shift in hormone treatment would be very interesting.

DR. BUTLER: I'm sure that Dr. Howard is pleased that he perhaps has finally been given the answer to the very pertinent clinical question that he asked yesterday: Is it safe to give a patient suffering the cardiac failure of K deficiency digitalis? I take it from what we have just been told that Szent-Györgyi has perhaps given us the answer. Digitalis blocks the uptake of K in a K-depleted heart muscle. Therefore, Dr. Howard may have the explanation of why such patients did not do well when they received digitalis.

DR. HOWARD: I agree with what Dr. Butler says. I believe that is a possible answer.

Recent Studies on the Role of Potassium in Hereditary (Familial) Periodic Paralysis

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PERIODIC PARALYSIS is the prototype of the clinical hypopotassemic states. Although the disorder was described as a clinical entity or syndrome approximately a century ago,[1] and was treated empirically with some degree of success with K salts as early as 1901,[2] hypopotassemia during the characteristic attacks of flaccid paralysis was not reported until 1934.[3] The relationship of disturbed K metabolism to pathogenesis and the therapeutic value of K salts did not become apparent until several years later.[4]

The paralytic attacks are apparently not preceded or accompanied by increased excretion of K by the kidney or by the gastrointestinal tract.[5] The total amount of K in skeletal and cardiac muscles before, during or after attacks is unchanged.[4,6] The abnormality appears to be primarily, if not solely, confined to muscle. Little is known concerning a possible alteration in the chemical or physical state of the intracellular K in relationship to paralytic attacks. Potassium excretion is actually diminished during attacks.

It has been demonstrated by various workers that agents or procedures capable of lowering the concentration of serum K abruptly, such as the administration of insulin or epinephrine or the excessive consumption of carbohydrate foods in readily available form, will induce flaccid paralysis of the extremities within a few hours in susceptible individuals. The peculiar defect in cellular physiology, which is responsible for this bizarre response, is not clearly understood. That the hypokalemia results from the diversion of K ions in the process of glycogenesis, as described by other participants in this symposium, was early suggested. This undoubtedly plays an important role in the ordinary spontaneous attack.

In recent intensive studies[7,8] on one member (a 15-year-old boy) of a large Minnesota family afflicted with classical hereditary periodic paralysis, the present authors attempted to obtain additional clinical and basic information regarding the nature of the disorder by determining the quantitative relationships between ingested carbohydrate (CHO) and K, on the one hand, and the occurrence of paralytic episodes, on the other, under a variety of conditions. Our findings may be summarized as follows: In preliminary tests on our voluntary experimental subject, it was found that the ingestion of 150 g. of glucose after a 14-hour fast regularly induced severe depression of the serum K level and also paralysis of the extremities within 2 or 3 hours. When he was in the same basic nutritive state, the injection of 40 to 50 units of insulin had the same effect within 4 to 5 hours. Ingestion of 5 g. of KCl (2.6 g. K) completely abolished the insulin- or glucose-induced paralysis within 20 to 30 minutes (Fig. 1).

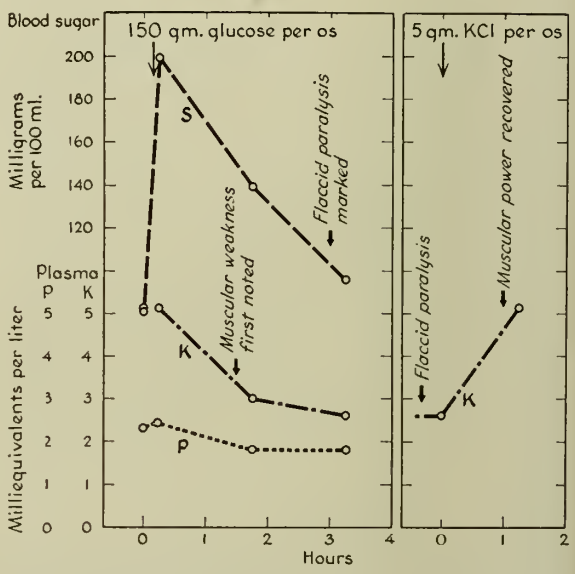

Fig. 1. Control test: typical response of S.B. to ingestion of 150 gm. of glucose in 450 ml. of water, given at 8:30 a.m. No other food since 5:30 p.m. of previous day. Sugar tolerance curve normal. Paralytic attack developed within 2.5 hours after glucose. Muscular power regained completely 45 minutes after administration of KCl by mouth. (Courtesy of *Metabolism* 1:116, 1952.)

Paralysis could be completely prevented by giving 1 g. of KCl by mouth every half hour over a 5-hour period, even after ingestion of 150 g. of glucose and the simultaneous injection of 50 units of insulin, a maximal provocation (Fig. 2). When 2 g. of K (3.81 g. KCl.) was ingested with 150 g. of glucose (G/K = 75), no attack was induced, but, when only 1 g. of K was taken by the patient with the same amount of glucose (G/K = 150) an attack of paralysis developed (Fig. 3).

These results, which were obtained on repeated trials, indicated that, under these conditions, the threshold value for the ratio, G/K, below which

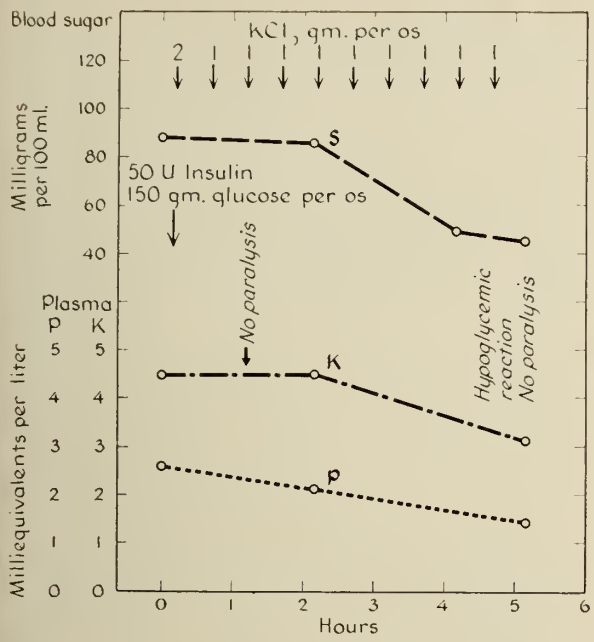

Fig. 2. Induction of paralytic attack by glucose and insulin prevented by administration of 0.5 gm. KCl every thirty minutes over five-hour period.

attacks would not occur was in the neighborhood of 75. Serum K values determined in the case of this patient on numerous occasions at or just prior to the onset of paralytic seizures varied between 2.6 and 3 mEq. per liter, indicating a characteristic, fairly constant threshold below which attacks could be expected.

On the basis of these findings from acute experiments, it was determined to ascertain the effects of various types of diet on the occurrence of changes in the serum K and paralytic attacks. The results were as follows: Fasting had the effect of completely abolishing spontaneous episodes of hypopotassemia and paralysis which had previously occurred almost daily while the patient was on the ordinary mixed diet of the hospital (see table I).

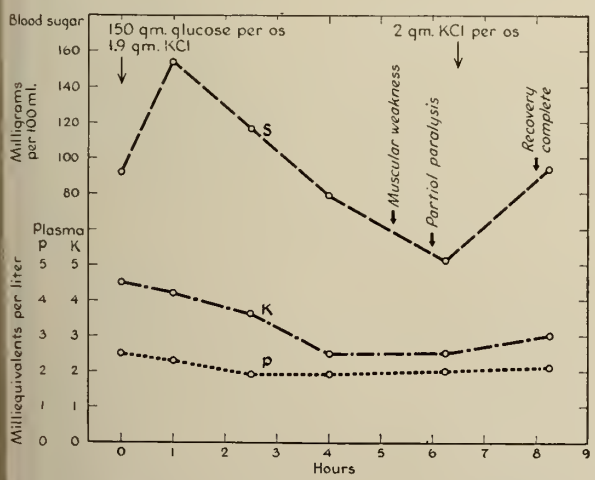

Fig. 3. When CHO/K equals 150, paralytic attack though delayed was not prevented. 1.9 gm. KCl (1 gm. K) insufficient to protect against 150 gm. glucose, whereas 3.8 gm. KCl (2 gm. K) by mouth prevented attack. Therefore, paralytogenic threshold lay somewhere between CHO/K of 150 and 75.

TABLE I

EFFECTS OF FASTING AND OF HIGH FAT, LOW CARBOHYDRATE (KETOGENIC) DIETS ON OCCURRENCE OF PARALYTIC ATTACKS

Diet	*Fasting*	*High fat, low carbohydrate low potassium*		
Protein (g./day)	0	84	84	76
Fat (g./day)	0	250	250	260
CHO (g./day)	0	33	21	10
F.A./G.	–	2.5	2.7	3.0
K (g./day)	0	0.91	0.91	0.64
K balance (g./day)	−1.79	+0.17	−0.12	−0.23
T.A.G./K	0	116	102	125
CHO/K	0	36	23	15
Period (days)	3	6	12	6
Paralytic attacks	0	2	8	2

The morning serum K rose from markedly subnormal levels before the fast to 5 mEq./l (normal), within two days, as a result of the fast. A straight milk diet (3 liters daily), having a preformed-carbohydrate to K ratio of 36, had a similar protective effect. When glucose was added to the milk diet in graded increments in succeeding periods to have the effect of increasing the G/K ratio, no paralytic episodes occurred, so long as this ratio was held at 68 or below. However, when it was raised to 80 or higher, attacks developed.

Ordinary mixed diets with moderately high carbohydrate content (378 g./day) did not permit use of a ratio as low as 63 (6 g. K daily), but the patient was entirely free from attacks when the ratio was decreased to 47 by addition of 2 extra grams of K daily. For this type of diet the threshold ratio lay, therefore, at a value intermediate between 63 and 47. The higher the CHO content of the diet, therefore, the greater is the K requirement per unit amount of carbohydrate ingested.

A high-protein, medium-fat, CHO-restricted diet proved to be tolerated very well with a CHO to K ratio intermediate between 50 and 75, even when the total K intake was reduced to 1 g. daily (see table II).

In contrast, the effect of a diet high in neutral fat, medium in protein and restricted in CHO content, whether ketogenic or non-ketogenic, proved to be as deleterious to this patient as did the high carbohydrate diet. A preformed-CHO to K ratio as low as 22 or even 15 permitted the development of hypopotassemia and paralytic episodes, even when the K intake was as high as 8.5 g. daily (see table III). So far as we are aware, this deleterious or "paralytogenic" effect of dietary fat in periodic paralysis has not been reported previously. A satisfactory explanation of this phenomenon might well be helpful

TABLE II

EFFECTS OF HIGH PROTEIN, LOW CARBOHYDRATE DIETS ON OCCURRENCE OF PARALYTIC ATTACKS

Diet	*High protein, low carbohydrate, medium fat*					
Protein (g./day)	170	170	170	170	170	170
Fat (g./day)	85	85	85	85	85	85
CHO (g./day)	5	10	25	37	50	120
K (g./day)	0.5	0.5	1.0	1.0	1.0	1.6
K balance (g./day)	−0.18	−2.18	−0.43	−0.18	−0.35	+0.22
T.A.G./K	204	214	122	134	147	136
CHO/K	10	20	25	37	50	75
Period (days)	19	1	4	2	3	2
Paralytic attacks	0	0	0	0	0	1

in the elucidation of the mechanism involved in the genesis of paralytic attacks. That K participates in the intermediary metabolism of fatty acids appears to us to be highly probable. Forced water drinking (up to 7200 ml. daily) and excessive ingestion of NaCl (60 g. daily) exerted no influence on serum K or paralytic attacks in week-long periods of observation.

TABLE III

EFFECTS OF HIGH FAT DIET WITH VARYING LEVELS OF POTASSIUM AND CARBOHYDRATE INTAKE ON OCCURRENCE OF PARALYTIC ATTACKS*

Diet	*High fat, varying carbohydrate and potassium*			
Protein (g./day)	84	84	84	84
Fat (g./day)	250	250	123	250
CHO (g./day)	20	187	86	200
F.A./G.	2.8	1	1	0.9
K (g./day)	0.91	8.50	3.89	9.10
K balance (g./day)	+0.08	+1.57	−0.07	+1.68
T.A.G./K	99	31	40	30
CHO/K	22	22	22	22
Period (days)	9	8	7	5
Paralytic atacks	8	7	0	0

*CHO/K constant.

Voluntary application of the results obtained from the present study has enabled our experimental subject, and his 8 similarly afflicted siblings as well, to remain entirely free from spontaneous paralytic attacks for prolonged periods. The diet prescribed for home use is characterized by its relatively high protein content and by a preformed-carbohydrate to K ratio maintained at or below 60. Its content of fat, as well as of carbohydrate, is restricted only moderately. Attacks have been found to recur within a few days when this dietary regimen is abandoned, unless a suitable amount of extra K is ingested.

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Phosphorylation Reactions Associated with Fatty Acid Oxidation

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In the metabolism of fats, as well as of carbohydrates, there are two separate phases of phosphorylation reactions deserving consideration. The first is the "priming" phase in which some high-energy phosphate compounds ($\sim PO_4$) are expended in order to activate the fatty acids for oxidative attack. The second is the phosphorylation reactions associated with the oxidative process in which inorganic phosphate is converted into $\sim PO_4$.

The necessity of $\sim PO_4$ for oxidation of fats was established by Leloir and Munoz[1] and by Lehninger.[2] In recent years several groups of workers have reported adenosine triphosphate to be unable to initiate fat oxidation and have indicated the necessity for simultaneous oxidation of carbohydrate intermediates.

With rat liver mitochondria,[3,4] or with the solubilized fatty acid oxidase prepared from acetone-desiccated mitochondria,[5] ATP alone is able to prime fatty acid oxidation. With the soluble enzyme, one mole of ATP is required to activate each mole of fatty acid.[5] This process involves activation of the carboxyl group so that it reacts with hydroxylamine. A detailed scheme of reactions for the activation and oxidation steps will be presented.

In studies with mitochondria it is essential to keep the fatty acid concentration low. Fatty acids of 8 carbon atoms or longer activate the adenosine triphosphatase of the mitochondria which results in depletion of phosphorylated coenzymes and loss of respiratory activity. This damage to the respiratory enzyme system can be partly overcome by adding K^+ to the incubation medium.[6]

Fatty acid oxidation to the stage of acetoacetate is coupled with the uptake of inorganic phosphate. When measured quantitatively, 2 moles of inorganic phosphate are esterified for each atom of 0 consumed.[4] These phosphorylations presumably occur

during electron transport over a series of coenzyme, flavoprotein and cytochromes to molecular oxygen.

Thus, for the case of palmitic acid oxidation to yield 8 two-carbon fragments, the expenditure of one mole of ~ P to activate the fatty acid returns a dividend of 14 × 2 or 28 moles of ~ P. If the 8 two-carbon units are combusted to CO_2 in the Krebs cycle, 8 × 12 or 96 additional moles of ~ P can be formed. These yields are calculated from experimentally determined efficiencies of phosphorylation during oxidation of individual Krebs cycle substrates.[4,7]

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DISCUSSION

DR. TARAIL: I should like to ask Dr. McQuarrie whether he thinks the observations of the German workers, Hubert Jantz,* who found that attacks of paralysis correlate better with a striking diminution of ultrafiltrability of K rather than with the change in total concentration of serum K have any validity. Jantz apparently has not reported his method for measuring ultrafiltrability — a procedure which, when rigorously done, is anything but simple. Nevertheless, the reported correlation may in part account for both the capriciousness and rarity of paralysis in patients with either deficiency or plethora of K.

DR. MC QUARRIE: The question asked by Dr. Tarail is a very pertinent and interesting one. If the findings by Jantz could be confirmed, they would undoubtedly take us another step toward an understanding of the problem of periodic paralysis. Unfortunately, we have made no study of the ultrafilterability of serum K in periodic paralysis.

DR. KINSELL: In one of the slides I showed yesterday (see figure 1), you may recall that in one of the diabetics who had not received any steroid therapy but who purposely was not adequately controlled and who, therefore, was in progressive K deficit, there was a major rise in blood ketones. (The patient was maintained on a chemcially constant formula diet throughout the study.)

When K was administered, two things occurred:

1. A major fall in ketones from approximately 25 to 5 mg. per cent.
2. A major fall in serum triglycerides.

Both the neutral fat and the blood ketones rose when the K was discontinued.

These observations might suggest that K is quite as essential to enzyme systems concerned with certain aspects of lipid metabolism as it is to enzyme systems concerned with certain aspects of carbohydrate metabolism. If the requirement of K for carbohydrate metabolism explains the precipitation of attacks of paralysis in patients receiving high carbohydrate intake, one might just

*Nervenarzt 18:360, 1947.

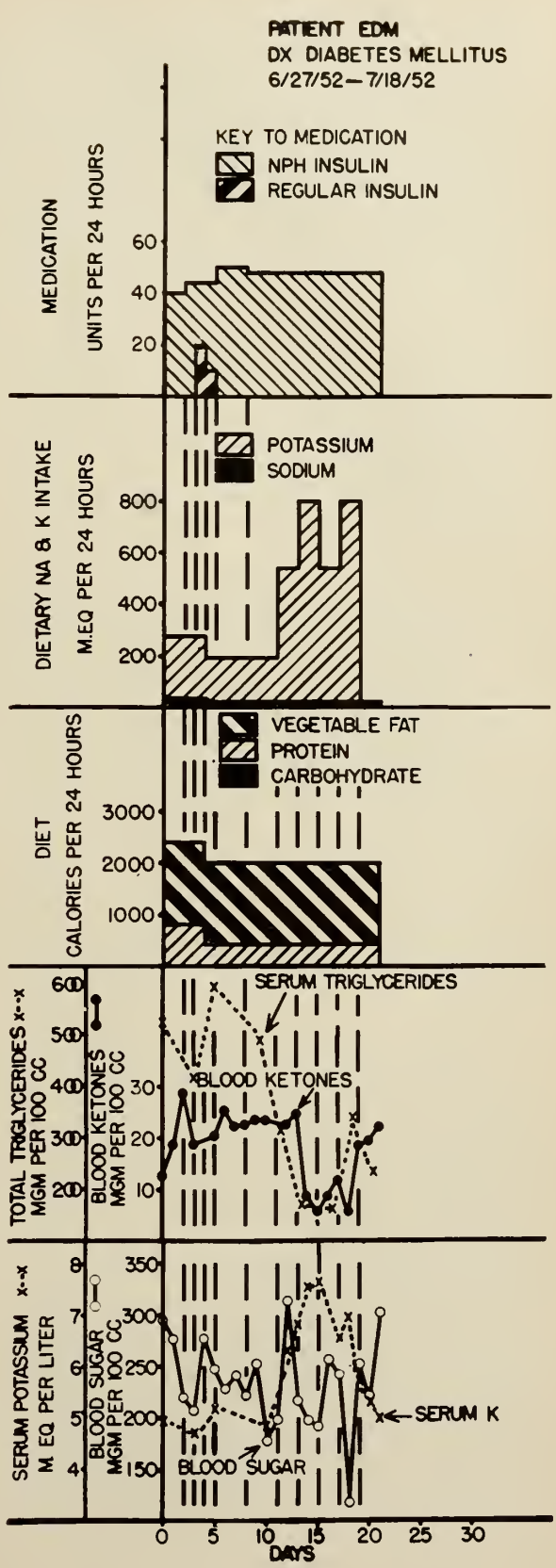

Fig. 1.

as readily explain the precipitation of an attack by the intake of a high fat diet, as Dr. McQuarrie has just reported.

DR. MC QUARRIE: I want to thank Dr. Kinsell and Dr. Lardy in particular for their discussions bearing upon our observation of the deleterious effect of the high-fat diet in periodic paralysis. These studies bearing on the role of K in the intermediary metabolism of fatty acids may conceivably explain the striking disturbance in K metabolism which we found. The results of further studies on the specific role of K in the enzyme reactions involved in fat metabolism will be anxiously awaited.

Dr. Kinsell asks if the serum K goes as low with the high fat diet as with the high carbohydrate diet. My reply is yes. And the small amounts of K involved in the shifts make me feel that the enzyme part of our story is the part that is missing.

DR. GARRETT: Why does the blood K level cause all this trouble when it goes down rather than the muscle K level. I didn't get that point?

DR. MC QUARRIE: Well, that brings up the question of the electrocardiographic changes, which I did not mention at all, as I should have done. On two occasions this patient showed ECG changes characteristic of the hypokalemic state during attacks. On other occasions no definite abnormality was seen despite the hypokalemia. It has been conjectured by some authors the ECG changes are better correlated with blood serum levels than with the skeletal muscle cell content of K. I wish we had some better way of determining whether that is the case. No one would be willing to attempt a heart muscle biopsy during a severe paralytic attack at the present time. I cannot tell which is the more important. We depend upon the serum K largely because blood is so easily available. Skeletal muscle analyses during attacks have given conflicting results.

DR. LARDY: I don't believe I have any additional comments. I agree with Dr. McQuarrie that we cannot yet extrapolate from what meager data we have about cell-free systems to the patients who display the interesting syndromes described during this symposium. I think we will have to do as much work in the field of fat metabolism as has already been done in the field of carbohydrate metabolism and then, if we all get together for another symposium, perhaps, we can explain some of these things.

The following illustrations appear through the courtesy of other publications: Page 218, Table 2: Willson, D. M., M. H. Power and E. J. Kepler: J. CLIN. INVEST. 19:701, 1940. Page 219, Table 3: Kepler, E. J., R. G. Sprague, O. T. Clagett, M. H. Power, H. L. Mason and M. R. Rogers: J. CLIN. ENDOCRIN. 8:499, 1948. Page 219, Table 4: Locke, William, G. M. Higgins and M. H. Power, unpublished data. Page 227, Figure 1: Talbot, N. B., J. D. Crawford and A. M. Butler: NEW ENGLAND J. MED., in press. Page 236, Figure 1: Case report by McNaughton and Burchell, J.A.M.A. 145:481-483, 1951. Page 239, Figure 1: Sharpey-Schafer, E. P., BRITISH HEART J. v5, 1943. Page 252, Figure 1: Ziegler, M. R. and Irvine McQuarrie: METABOLISM 1:116, 1952.

Lancet Editorial

Potassium Metabolism Symposium

MEDICAL KNOWLEDGE derived from controlled observation and experimentation in the clinics and laboratories of the civilized world continues to expand in volume at an accelerated tempo. A significant fraction of such new information becomes of direct importance to practicing physicians sooner or later, but in many areas of special study, there is an unfortunate lag between original discoveries and their application.

Early publication of the "raw material" from which clinical medicine is fabricated, is an invaluable service to all modern physicians who wish to know the scientific basis of their knowledge and practice. When THE JOURNAL-LANCET undertook publication of the proceedings of a recent Symposium on Potassium Metabolism held at the University of Minnesota, it was motivated primarily by a genuine desire to promote early dissemination of valuable new data.

The specific physiological roles of potassium in the cellular economy and the clinical manifestations of hypokalemia and hyperkalemia are many, as indicated in the summaries of papers published in the May and June issues of this journal. Reading the original abstracts and related discussions will induce most of us to view our daily clinical experiences with a fresh perspective and increased insight.

IRVINE MCQUARRIE, M.D.,
Department of Pediatrics,
University of Minnesota

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.*

Clinicopathological Conference

Minneapolis Veterans Hospital*

Edited by James F. Hammarsten, M.D.
Assisted by Robert I. Lubin, M.D. and
Donald Fry, M.D.

PRESENTATION OF CASE

A 61-year-old park board employee was admitted on February 4, 1952, because of gastrointestinal hemorrhage.

He was disoriented at the time of admission and a meager history was obtained from friends. They stated that he had been under a physician's care for a bleeding ulcer. The patient had been a severe alcoholic for many years with increased alcoholic consumption for four years.

Later when the patient was oriented (vide infra) more information was obtained. He stated that he had been well until the latter part of November 1951 when he noted weakness followed by hematemesis of 1 pint and by tarry stools. He consulted a physician. X-ray studies of the gastrointestinal tract disclosed an ulcer, according to the patient. (These x-ray films were interpreted as negative by our radiology department.) A bland diet was prescribed and he improved. He could recall nothing about the week prior to admission.

The past history was entirely negative. He denied gastrointestinal symptoms. He admitted drinking 1 to 2 ounces of whiskey daily.

Physical examination showed an obese disoriented man. There was bilateral arcus senilis. Sonorous râles were heard over the anterior chest and a few moist râles at the right base posteriorly. The apex impulse was found in the midaxillary line. A tarry stool was obtained by rectal examination.

The temperature was 103° F. rectally, the pulse rate 130 per minute, and the blood pressure 128 mm. Hg systolic and 88 diastolic.

The hemoglobin was 7.7 gm. per 100 ml. and white blood cell count 13,250 per mm.^{3} with 64 per cent neutrophils, 32 per cent lymphocytes, and 4 per cent basophils. The erythrocyte sedimentation rate was 31 mm. in 1 hour. A urinalysis was negative. A blood Kahn was negative. The 1 minute serum bilirubin was 0.2 mg. per 100 ml. and the total 1.3. The bromsulfalein retention was 45 per cent in 45 minutes. The prothrombin time was 14.5 seconds with a control of 13.5. The stool was positive for occult blood. An x-ray film of the chest showed enlargement of the heart of the left ventricular type.

He was given 1500 cc. of whole blood. The following day he was still deeply comatose and was visibly icteric. The hemoglobin had increased to 9.7 gm. per 100 ml. He was given 2 liters of blood. The serum sodium was 140.9 mEq. per liter, potassium 4.41 mEq. per liter, chloride 111 mEq. per liter, CO_2 23 mEq. per liter, and blood urea nitrogen 20 mg. per 100 ml. On February 6, the hemoglobin had increased to 12 gm. per 100 ml. The 1 minute serum bilirubin was 5.1 mg. per 100 cc. and the total 8.6 mg. He was hyperventilating and had a clonic convulsion. The Babinski was positive bilaterally. He continued to hyperventilate and on February 7 had frequent muscular twitchings. The next day the potassium had decreased to 3.91 mEq. per liter and the CO_2 to 18.9 mEq. per liter. The sodium and chloride were not changed. The spinal fluid was normal and serum calcium was 9.8 mg. per 100 ml.

He remained in coma, continued to hyperventilate, had frequent muscular twitchings and occasional convulsions, and remained febrile. By February 11 the potassium had decreased to 3.45 mEq. per liter and the CO_2 to 14 mEq. per liter. The chlorides had increased to 117.6 mEq. per liter and the blood urea nitrogen to 39.5 mg. per 100 ml. He responded for the first time, was able to answer questions, and ate. He had been receiving intravenous glucose almost daily. On February 11 after the patient was conscious potassium chloride was added to the intravenous fluid for the first time.

On February 12 the stools, which had shown positive guaiac tests, contained no occult blood. He again lapsed into coma. He was responsive, afebrile, and breathing normally on February 13 and continued to improve thereafter. The 1 minute serum bilirubin was 0.7 mg. per 100 ml. and 1.6 mg. total. The cholesterol was 119 mg. per 100 ml. with 77 mg. in the esterified fraction. The alkaline phos-

(Continued on page 262)

*Published with approval of Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Infant Development (the embryology of early human behavior), by Arnold Gesell, M.D. 1952, New York, Harper and Bros. Pp. 108. $3.50.

This is a wonderful book of 108 pages which every pediatrician and many physicians in various fields of endeavor ought to own and study. As most physicians know, Dr. Gesell has spent 35 years studying the mental development and the growth of infants.

This book is necessary equipment for all persons who have to decide whether a given child is developing normally or is mentally retarded. The doctor shows just what an infant should be doing at the end of every short period of its life. He shows how the child lies at first somewhat on its side, and how he soon turns over on his back and begins to move his hands. It shows how he begins to grasp a block of wood and later learns to build a pile of blocks. At a certain time he smiles and crows and creeps and stands in his playpen. Later he learns to draw figures, he learns to talk and to walk.

To the Freudian psychiatrist these studies of Gesell's should be disturbing because they show that in intrauterine life and for weeks and months afterward, the child's brain is slowly developing and becoming capable of performing new functions. Some Freudians talk as if they believed that even in intrauterine life the child's brain is fully developed. It certainly isn't.

W.C.A.

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Use of Antibiotics in Tropical Diseases. Annals of New York Academy of Sciences. Vol. 55, Art. 6, pp. 967-1284. Published in New York by the Academy, December 30, 1952.

This is a splendid volume containing as it does many authoritative articles on the present status of treatment of many diseases such as epidemic typhus, amebiasis, the rickettsias, plague, dysentery, oroya fever, the relapsing fevers, and the several non-venereal spirochetoses.

Probably few physicians in America know that in Iraq and Arabia most of the people and particularly their children, suffer from a contagious non-venereal type of treponematosis called bejel. If not treated, it lasts for years and causes a certain amount of disability. In other parts of the world yaws causes a great amount of disability. It also is a non-venereal disease produced by a spirochete indistinguishable under the microscope from that of syphilis. In many parts of Latin America there is a common disease called pinta which is also due to a spirochete. Fortunately these diseases are now easily cured with a deposit of penicillin.

The reviewer has always wondered if the great flare-up of syphilis in Europe in the last half of the 15th century might not have been due to the spread of a changed form of bejal which may have been endemic for thousands of years in the Near East. W.C.A.

Doctor in the House, by Richard Gordon. 1952, London, Michael Joseph. 190 pages.

Between March 1952 and October 1952, this amazing account of an English student's medical training went through ten editions. The action takes place mainly in St. Swithin's Hospital, and a preparatory note says, "St. Swithin's Hospital does not exist; neither do its staff, students, nor patients." If we must believe the note, we can only add, "More's the pity."

It is not a book for the waiting-room table nor to give members of anti-medical societies. Its humor is medical, British, and incredible. The pictures of the medical school, the professors, the patients, the nurses, and the medical students come precariously near to being recognizable. On surgical rounds, the medic records, "I gazed at the abdomen for a whole minute but it appeared no different from any that might be seen on Brighton Beach." Of his clerkship in midwifery he tells us that "My predecessor, a tall, fair-haired, romantic-looking man, called Lamont, had been so moved by his experiences he was on the point of breaking off his engagement."

Doctor in the House does not discuss the panel system nor the economic status of English medicine, but it will give you an hour's entertainment and more than one guffaw.

O. W. del P.

Practical Dermatology (for medical students and general practitioners). By George M. Lewis, M.D. 1952, Philadelphia, Pennsylvania, W. B. Saunders Co. Pp. 328.

Dr. George M. Lewis is professor of clinical medicine (dermatology) at Cornell University Medical College, and attending dermatologist of the New York Hospital.

As he says, this book was designed as a text for medical students, a practical guide for general practitioners, and an aid in orientation for other specialists. It was designed to be concise and well illustrated. About one-sixth of the cases seen in general practice are dermatologic in nature. The general practitioner and internist can at times be helped if he knows something about dermatology, because skin lesions appear with a number of generalized diseases.

The book is concise and to the point. It is well written and beautifully illustrated, and there is a good chapter on treatment and on the drugs that are commonly used.

For the man who wants a short but adequate book on dermatology this is excellent. W.C.A.

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Essentials of Infant Feeding for Physicians, by Herman Frederic Meyer, M.D. 1952. 249 pages. Springfield, Illinois: Charles C Thomas.

Dr. Meyer draws a distinction between infant feeding and infant nutrition. The latter term he uses to refer to the scientific study of the infant's need for and utilization of food elements. The practical application of the research findings is what he means by the term infant feeding, and it is with this that his book is concerned.

Little in the way of practical advice in infant feeding could be added to this book. There are detailed tables of the nutritive elements of all proprietary infant food products available in 1952. There are adequate instructions for the calculation of formulas. Nursing bottles are listed and described. The discussion of breast feeding is one of the best this reviewer has encountered. Throughout the book there runs a good-humored commentary on all aspects of infant feeding.

Any physician who needs help in the important everyday problems of infant feeding — at home or in the hospital — can likely get it from Dr. Meyer's book. S.F.B.

American College Health Association News

One hundred fifty-seven persons registered at the annual meeting in Columbus, Ohio. This number is approximately the same as the number of registrants at the Boston meeting. Eighty-one member institutions were represented and seven non-member institutions. There were also persons present who are not associated with colleges and universities. An outstanding event occurred — every local section was represented! The majority of registrants were physicians, but all other disciplines were represented, including dean of men, dean of women, dentist, medical technician, environmental health examiner, nurses, and health educators.

The newly-elected officers are: President: Dana Farnsworth, M.D., Massachusetts Institute of Technology; president-elect: Norman S. Moore, M.D., Cornell University; vice-president: John Wilce, M.D., Ohio State University; secretary-treasurer: Edith M. Lindsay, Ed.D., University of California, Berkeley Campus; council members for three years: John W. Brown, M.D., University of Wisconsin, and William E. Taylor, M.D., Southwest Missouri State College.

The professional program was divided between considerations of how health services could improve their usefulness to the rest of the college and clinical conditions of interest to all physicians. In the latter category papers by Dean C. A. Don on blood disorders of college students and Dr. George J. Hamwi on endocrine problems were outstanding. Dr. Norman Moore of Cornell University reported that a survey of college health facilities is now underway which promises to be the most comprehensive of any that has been done up to this time. The survey findings will be of inestimable value in planning college health programs in the future.

The tentative plans for the Fourth National Conference on Health in Colleges to be held in New York City on May 5, 6, 7, and 8, 1954, at the Hotel Statler, were outlined by Dr. Dana L. Farnsworth.

The Association was particularly appreciative of the magnificent hospitality shown by Dr. John W. Wilce and his able colleagues.

NEW DIRECTOR-GENERAL APPOINTED FOR WORLD HEALTH ORGANIZATION

Dr. M. G. Candau was appointed recently as Director-General of the World Health Organization. He has worked extensively in the field of public health education. He holds the position of Public Health Officer in the State of Rio de Janeiro, Brazil, and of Assistant Professor of Hygiene of the School of Medicine of the State of Rio de Janeiro. He is a member of the American Public Health Association, of which he was Vice President in 1949-50, the Royal Society of Tropical Medicine and Hygiene (London), the Inter-American Association of Sanitary Engineering, and other scientific societies.

Program of the Rocky Mountain Radiological Society Meeting Denver, August 20, 21, 22, 1953

GUEST SPEAKERS

"Gastric Carcinomas, Missed" (25 minutes), "Muscular Contraction Paterns in Certain Esophageal Conditions" (25 minutes)—*Frederic E. Templeton, M.D.*, Seattle, Washington.

"Roentgen Findings in Hemochromatosis" (30 minutes), "Roentgen Studies in Patients with Mitral Disease" (30 Minutes)—*Merril C. Sosman, M.D.*,* Boston, Massachusetts.

"Malacic Diseases of Bone" (30 minutes), "Myelofibrosis and Myelosclerosis" (20 minutes)—*David G. Pugh, M.D.*, Rochester, Minnesota.

"Reminiscences of Forty-four Years of Radiology in the British Army Medical Service" (30 minutes), "Selected Medical and Surgical Radiological Problems in the Royal Army Medical Corps" (30 minutes)—*Brig.D. B. McGrigor, OBE, MB ChD Hon F.S.R. Legion of Merit*, London W 1, England.

"The Skeletal Features of Cargoylism (Dysostosis Multiplex)" (30 minutes), "Pulmonary Cysts of Early Infancy; their natural regression" (30 minutes)—*John Caffey, M.D.*, New York City, New York.

"Urethrocystography in Children" (30 minutes), "Value of Heart Volume Determinations" (30 minutes)—*Dr. Sven Roland Kjellberg*, Stockholm, Sweden.

BANQUET SPEAKER: *Edward J. McCormick*, Toledo, Ohio, President of the American Medical Association. (Assumes presidency in June).

SPEAKERS BY INVITATION

1. "Tumors of the Small Bowel" (20 minutes)—*R. F. Nuessle, M.D.*, Bismarck, North Dakota.
2. "Protection of Radiological Personnel During Diagnostic Procedures" (20 minutes)—*Vincent W. Archer, M.D.*, University, Virginia.
3. "Lesions in and About the Second Portion of the Duodenum" (20 minutes)—*Lester D. Shook, M.D.*, Kansas City, Missouri.
4. "Obstructive Lesions of the Gastrointestinal Tract in Infants" (30 minutes)—*Edward B. Singleton, M.D.*, Houston, Texas.
5. "Carcinoma of the Mouth and Neck" (one hour)—*Charles Martin, M.D.*, Dallas, Texas.
6. "Recent Developments in Atomic Energy of Interest to Radiologists" (30 minutes)—*Paul C. Abersold*, Oak Ridge, Tennessee.
7. Pediatric Radiological Paper by *Walter Wasson, M.D.*, Denver, Colorado.
8. Pediatric Radiological Paper by *John Bouslog, M.D.*, Denver, Colorado.
9. Pediatric Radiological Paper by *Robert Parker Allen, M.D.*, Denver, Colorado.
10. "Isodose Data for Intra-Cavity Roentgen Therapy" (20 minutes)—*E. Dale Trout, B.D., Sc.D.*, Milwaukee, Wisconsin.
11. "The Roentgen Manifestations of Early Joint Disease" (20 minutes)—*Everett L. Pirkey, M.D.*, Louisville, Kentucky.
12. "The Roentgen Findings in Strangulation Obstruction of the Small Bowel" (20 minutes)—*Harry Z. Mellins, M.D.*, Detroit, Michigan.
13. "Low Back Pain from the Viewpoint of the Radiologist" (20 minutes)—*Ira H. Lockwood, M.D.*, Kansas City, Missouri.

*Dr. Sosman is appearing through the courtesy of the North Dakota Radiological Society.

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(Continued from page 257)

phatase was 51 King-Armstrong units, cephalin flocculation plus-minus in 24 hours and 1 plus in 48 hours, thymol turbidity 3.5 units, and zinc sulfate turbidity 12 units. The serum protein was 6.3 gm. per 100 ml. with 4.0 gm. albumin and 2.3 globulin.

The potassium and CO_2 rose to normal values and the blood. urea nitrogen decreased to 15 mg. per 100 ml.

The patient ate well and showed no further gastrointestinal bleeding. On February 19 the 1 minute serum bilirubin was 1.4 mg. per 100 ml. and 2.3 total, the corrected bromsulfalein retention 37.5 per cent, cephalin flocculation 0 in 24 hours and plus-minus in 48, thymol turbidity and zinc sulfate turbidity unchanged, and alkaline phosphatase 65 King-Armstrong units. The blood pressure remained about 140 mm. Hg systolic and 90 diastolic.

An electrocardiogram was normal. X-ray studies of the gastrointestinal tract after two barium meals and a barium enema were negative.

The white blood cell count decreased to 3700 with 60 per cent neutrophils, 37 per cent lymphocytes, and 3 per cent eosinophils. The 1 minute serum bilirubin increased to 2.5 mg. per 100 ml. and 4.1 total. The flocculation tests were unchanged. The cholesterol increased to 207 mg. per 100 ml. with 139 mg. in the esterified fraction. The urine urobilinogen was 8.7 mg. in 24 hours. A 1 plus glycosuria and a fasting blood sugar of 107 mg. per 100 ml. were discovered.

He was ambulatory, eating well and asymptomatic on March 3, 1952, prior to discharge.

Second admission (March 14, 1952). He was again admitted in coma. An interval history was not available. The physical examination was similar to that of the previous admission. The sclera were icteric. Tarry stool was found by rectal examination. The pulse rate was 108 per minute, the temperature 99.6° (rectally), and the blood pressure 130 mm. Hg systolic and 70 diastolic.

The hemoglobin was 6.3 gm. per 100 ml. He was given 2500 cc. of whole blood. The hemoglobin rose to 8.8 gm. per 100 ml. He remained in coma and again developed hyperventilation.

He died 30 hours after admission.

DISCUSSION

DR. FREDERICK HOFFBAUER*: Despite the fear in my heart when I discuss one of these cases, this did appear to be a fairly straightforward case.

It involves the problem of massive gastrointestinal hemorrhage, which immediately brings up the question of bleeding peptic ulcer versus bleeding from esophageal varices as the two most likely causes of massive gastrointestinal hemorrhage. I would think the data favor the probability of bleeding from varices. In favor of that hypothesis is the clinical

*Associate professor of medicine, University of Minnesota.

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(Continued from page 262)

evidence of liver disease, i. e., coma and jaundice.

The failure of the radiologist to demonstrate a peptic ulcer on three examinations is against the diagnosis of ulcer. A radiologist can obtain an accuracy of 95 per cent in the diagnosis of peptic ulcer, but his ability to demonstrate varices probably does not exceeed 50 per cent. I was interested to note the date of the gastrointestinal studies in relation to the episodes of bleeding. Shortly after a severe hemorrhage with reduction in blood volume, the radiologist is less apt to visualize varices. These examinations were performed when the blood volume was restored so that is not an excuse for the failure to find varices. Nevertheless, I believe they were present.

In any case with suspected esophageal varices one must consider whether it is extrahepatic-portal vein block or intrahepatic The evidence favors intrahepatic block for the development of portal hypertension. The performance of the bromsulfalein test is an aid to the differential diagnosis of massive gastrointestinal hemorrhage. This has been pointed out by Zamcheck and coworkers.[1] They observed that patients with peptic ulcer, despite blood pressures in shock levels, seldom exhibit a bromsulfalein retention of greater than 20 per cent; whereas patients with varices and cirrhosis usually show elevated bromsulfalein values.

The usual abnormalities of serum protein are lacking in this patient. He did not have hypoalbuminemia or hyperglobulinemia. This is somewhat unusual and I do not have an explanation for it. The occurrence of an elevated alkaline phosphatase in a patient with cirrhosis makes one suspect primary carcinoma of the liver developing in a cirrhotic liver. But I do not see any other evidence for that diagnosis in this patient.

I think the most likely diagnosis is diffuse cirrhosis with bleeding from esophageal varices. The absence of protein changes, absence of a palpable spleen, and inability of the radiologist to demonstrate varices all are disturbing, but do not dissuade me from my original diagnosis.

DR. HAMMARSTEN: Dr. Nesbitt saw this patient when the man was in coma. He shook his head, said he didn't think the man had hepatic coma, and then left for Florida. Fortunately he returned today and I was wondering if he would care to continue that discussion.

DR. NESBITT: I saw this man a number of times during his initial admission but not at the time of his final admission. I was extremely puzzled and was reluctant to accept this as the picture of hepatic coma. I was a little more disturbed than Dr. Hoffbauer by the laboratory tests. In patients with hepatic coma all of the usual liver function tests are rather grossly abnormal, but this man had perfectly normal flocculation tests.

The thing that disturbed me the most, however,

was the potassium level. We have found very low values for potassium in hepatic coma.[2] When he was in profound coma, his serum potassium was 4.41 mEq. per liter. Then to our surprise, when his potassium was the lowest, he roused and came out of coma.

I must say I am unable to make a definite diagnosis. In desperation I am inclined to suspect that he may have had an intracranial lesion, either on a vascular basis or a metastatic neoplasm.

The elevated alkaline phosphatase also makes me suspect a hepatoma, which could have metastasized to the brain. That would be most unusual. Hepatomas usually metastasize regionally first and then to the lungs. I think the gastrointestinal tract has not been excluded as a site of neoplasm to account for the bleeding. Other possibilities would be neoplasm of the pancreas or the ampulla.

A RESIDENT: I would like to ask Dr. Hoffbauer if he has seen patients with hepatic coma and normal flocculation tests.

DR. HOFFBAUER: I don't recall any.

DR. HAMMARSTEN: Dr. Nesbitt, would the determination of the pyruvic acid level in the blood or spinal fluid aid in the diagnosis of coma suspected to be on the basis of liver disease?

DR. NESBITT: Yes, it would. We found the blood and spinal fluid pyruvic acid invariably elevated in hepatic coma.[3] It is also elevated in starvation and deficiency states.

DIAGNOSES

Clinical diagnosis: Hepatic cirrhosis, bleeding from esophageal varices.

Dr. Hoffbauer's diagnosis: Hepatic cirrhosis, bleeding from esophageal varices.

Anatomical diagnosis: Islet cell carcinoma of the pancreas with erosion through the posterior wall of the stomach.

PATHOLOGICAL DISCUSSION

DR. GLEASON: The liver weighed 1475 gm. and showed no evidence of cirrhosis. The spleen weighed 150 gm. and appeared normal. There was a large mass which replaced the pancreas. The mass was adherent to the posterior wall of the stomach and ulcerated through the wall. This must have been the source of hemorrhage. The big surprise is the histological appearance of the mass. It is an islet cell tumor of the pancreas. There were no metastases, but the histological features would make me call it an islet cell carcinoma of the pancreas.

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The Family and Children's Service, serving Minneapolis, Hennepin County and Columbia Heights, has developed a half-pocket-sized 8-page booklet in two colors that outlines the scope and services of the organization. These consist of consultation and assistance to families and individuals who need help in solving personal and family problems, including marital adjustments, relations between parents and children, personality adjustment, as well as special services to children in need of remedial attention. Foster home, boarding care, homemaker service or other treatment is provided for children in certain instances.

The title of the booklet is *"What's Your Family Picture?"* and it is intended that it be distributed to and by physicians and others in authoritative relationship to families. Call Main 5275 – ask for Family and Children's Service, and instruct them to send you several copies, one to be read by you and retained and the others to be handed judiciously to those of your patients who would seem to need such information or are in position to pass it on where it will do the most good.

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RODNEY F. STURLEY, M.D.

St. Paul, Minnesota

THE USE of cesarean section in parturient women represents one of the controversial subjects in modern obstetrics. The original cesarean sections were done exclusively in laboring women, but only when the outcome appeared almost surely fatal for the mother. By this extreme means the fetus was given this opportunity to live.

As medicine progressed, the procedure became less hazardous, particularly when done electively. The risk to the mother was greatly increased if the patient was in labor or the membranes ruptured. Because of the added risk, every effort was made to complete delivery from below. In the presence of certain obstetrical complications, the fetus was often destroyed, either during the prolonged labor or during the birthing process, particularly when accomplished by obstetrical procedures such as version and extraction, difficult midforceps, or forceps rotation. The mothers usually survived, but often suffered severe lacerations resulting in anemia. Often the patients developed dangerous infections. Not infrequently these experiences produced a psychic trauma severe enough to develop intense fear of future pregnancies.

The use of cesarean section after the onset of labor resulted in the introduction of infection into the peritoneal cavity. Patients who were potentially or actually infected, and in whom existed absolute indications for cesarean section, poised a problem for the early obstetrician. It was partially solved by the utilization of operative procedures designed to reduce the amount of contamination to the peritoneal cavity. This was achieved by the use of cesarean section followed by hysterectomy, by the employment of the extraperitoneal approach to the lower uterine segment, or by the use of the lower uterine segment double-flap technique.

While improvements in surgical technique were great steps forward, the infection or morbidity rate was still too high to make the operation desirable for other than absolutely essential cases. Further advances were necessary before the section of potentially infected mothers would be safe.

The introduction of modern antibiotics and chemotherapy requires re-evaluation of the management of obstetrical difficulties. The additional safety offered by the use of these medications has resulted in an increased use of cesarean section. This is particularly true of problems arising during labor. The decreased risk to the mother affords the obstetrician an opportunity to reduce maternal trauma and improve fetal survival. I have in mind the care of the neglected transverse presentation where in large series delivered from below, the fetal mortality was 40 per cent. A comparable series delivered by cesarean section resulted in a fetal mortality rate of six per cent. This does not take into consideration the danger of rupturing the uterus during the attempt to deliver these women by version and extraction, a time-honored obstetrical procedure for this complication.

The development of cesarean section has been directed largely toward the prevention of infection. I have already mentioned the surgical efforts to decrease peritoneal contamination, namely the use of the hysterectomy following section and the use of the extraperitoneal approach. These procedures have been widely used. In some clinics they are always used in the case of the infected or potentially infected woman. They have very definite disadvantages. The disadvantage of hysterectomy is obvious. Too often the obstetrical patient in greatest trouble

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is the young and primiparous individual. Hysterectomy here would be disastrous. The extraperitoneal approach is only too often transperitoneal by virtue of perforations inadvertently made during the dissection. In addition, there is considerable danger of damage to the urinary tract, particularly the bladder. With these thoughts in mind, and with the advent of chemotherapy and antibiotics, many recent operators have elected to use only the lower uterine segment cesarean section. Not a few authorities have made the statement that they see very few instances where the use of the more involved procedures is necessary, though most of them reserve the right to use either of the operations for some peculiar situation.

REVIEW OF THE LITERATURE

Kobak, Fields, and Turow reported a series of 100 cases. Fifty-three cases of the group were considered potentially infected, and 47 were actually infected as evidenced by temperature elevation, chills, purulent and foul amniotic fluid. They performed only lower uterine segment cesarean sections combined with the use of pencillin and, in a few cases, additional streptomycin and sulfonamides. There were no deaths. Using the usual method of calculating maternal morbidity as perscribed by the National Committee on Maternal Welfare, i.e., any temperature elevation of 100.4 or better in any two 24 hour periods exclusive of the first 24 hours, they had a morbidity rate of 45 per cent. They compared this figure with the morbidity rate of a series of 110 elective sections receiving no antibiotics. Here the morbidity rate was 31 per cent. It was their conclusion that should the above experience be confirmed by others, there will be little need for the use of the extraperitoneal approach or the hysterectomy following section as a prophylactic measure against peritonitis.

Dantuono reported a series of 57 patients operated at Bellevue Hospital of New York City. All patients had been in labor 30 hours or more. All but three had membranes ruptured. Morbidity was considered present if the patient had a temperature of 100.0 or more in two 24 hour periods exclusive of the first 74 hours following surgery. On this basis there was a morbidity rate of 54 per cent. There were no deaths. The patieents were givn sulfonamides and/or penicillin prophylactically during labor and after surgery. All of these cases were operated upon using the lower segment section.

D'Esopo, in 1950, made a complete review of cesarean sections at Sloane Hospital for Women during the period 1942-1947. There were 1,000 consecutive cases with one death which was unrelated to the operation. The author emphasizes the importance of substituting delivery from above for traumatic delivery from below. It is his opinion that the increased incidence of cesarean section has resulted in less trauma to mother and child without sacrifice of maternal life. They had 151 cases in which the uterus was potentially infected. The lower uterine segment section was used in 117 cases. They are of the opinion that the infected patient can be relatively safe with the use of the lower uterine segment section as against the use of the extraperitoneal cesarean section or cesarean-hysterectomy. They did feel that the latter procedures might have a definite place, but that their use was largely eliminated by the use of the lower segment section. All of their cases were given penicillin during labor and after delivery.

One year before this final report, D'Esopo showed in his survey of cesarean sections at Sloane Hospital that there was a definite trend toward the more frequent use of cesarean sections and a decrease in the more formidable vaginal deliveries. He also showed some tendency toward the increased use of section in the treatment of placenta praevia, breech presentation, and cephalopelvic disproportion. A new indication for the use of section was listed at this time in the treatment of prolapsed cord. He is of the opinion that the tendency of shifting from the difficult vaginal delivery to delivery by the abdominal route is justified by the decreasing maternal risk, and further justified by the decreased trauma to the mother, not to mention the child. Against this, it may be said that unnecessary sections will be done when vaginal delivery might have been effected easily and safely. Since uncomplicated vaginal delivery will always be less dangerous to both mother and child, the unnecessary cesarean section done in ignorance or for convenience cannot be justified.

Douglas, in 1946, made an extensive study of puerperal infection. He felt the infection began with the onset of labor. The rapidity of growth is accelerated greatly if the membranes are ruptured. The quality of the labor does not influence the development, it being largely a factor of time. He felt also that with premature rupture of membranes, if the patient were kept at rest, infection was much less likely to occur. At this time he made the statement that cesarean section should not be performed after 8 to 12 hours of labor. He was of the opinion that sulfadiazine or sulfadiazine and penicillin, when given early in labor, would decrease the incidence of infection. Just two years later, he makes the statement that with early prophylactic drug therapy, a longer trial of labor may be used without danger. The control of infection by these prophylactic agents broadens the safe employment of transperitoneal section and reduces the need for extraperitoneal section and section hysterectomy. In their series of cesarean sections for 1946 they had 136 operations with an over-all morbidity of 34 per cent. In a series of 15 cases operated by lower uterine segment cesarean section following 24 hours of labor, about a third of them were morbid. All the cases were treated with sulfadiazine and penicillin prophylactically. He states that the main indication for surgery was desultory labor with unsatisfactory progress. Disproportion was rarely recognized.

In answer to those who would criticize the more liberal use of cesarean section in the treatment of

obstetrical complications which have been treated in the past by the various time-honored obstetrical maneuvers from below, I should like to mention the study of Watt of Canada. He studied all the cases of ruptured uteri in the Toronto General Hospital for 1927 through 1946. During this period there were 17,455 deliveries with fifteen cases of ruptured uteri. Nine of these ruptures occurred following some obstetrical maneuver. Six of the ruptured uteri occurred following the use of version and extraction, two with high forceps extraction, and one with breech extraction. It further resulted in eight stillborn fetuses, three dead mothers, and two vesicovaginal fistuli. He summarizes by stating that there must be a better solution, and suggested that at least the procedure of version and extraction in the management of other than bleeding emergencies and the delivery of the second twin be abandoned for more frequent use of cesarean section. One might counter these statements by saying that the procedure was used in only the worst cases. During the same 20 year period, version and extraction was attempted (after the seventh month and for other than the second twin) on 52 occasions and resulted in one maternal death, a fetal mortality of 63 per cent, seven ruptured uteri, and two vesicovaginal fistuli. This was not a very impressive record. He concludes that with the increasing safety of lower uterine segment section combined with the use of antibiotics and chemotherapy, we can become more "radical" in our treatment of complications such as transverse presentation, brow, and high occiput posterior position.

Watt, in the same article, further states that of the five cases of ruptured uteri through cesarean scars, all were in the classical cesarean scar. In a survey of the literature, he quotes a collected series of 26 ruptured uteri in old cesarean scars, two of which occurred in lower uterine segment scars. This certainly stands as a strong argument for the abandonment of the old classical cesarean section and the use of the safer lower uterine segment section.

LOWER UTERINE SEGMENT CESAREAN SECTION

Our own experience has demonstrated to our satisfaction that the lower uterine segment cesarean section can be used today by the obstetrician in the management of serious obstetrical complications often not recognized until labor has been in progress many hours. Many of these cases if not handled by section would result in an unfavorable outcome, particularly with respect to fetal survival.

A survey of patients treated in the past five years has shown that the use of the lower uterine segment cesarean section combined with antibiotics and blood transfusion has resulted in only a small increase in the morbidity rate over that of elective section, even though the sections in many instances were done long after the onset of labor. This factor, together with the absence of mortality and a 100 per cent fetal survival, has convinced us that the procedure is sound and, further, that the use of cesarean-hysterectomy and extraperitoneal cesarean section are seldom needed.

During the past five years we have operated 190 cases by cesarean section (table 1). The morbidity rate for the entire study was 19 per cent. Forty-six of these patients were operated upon after the onset of labor. In this group, the morbidity rate was found to be 26 per cent. If we eliminate the four cases operated upon using the classical incision, the morbidity rate is 24 per cent. The morbidity rate for elective lower uterine segment sections was 14 per cent. Since we do not recommend classical cesarean section under any circumstances, it does not seem irregular to remove them from the final figures. There were no maternal deaths in the entire series. There were no fetal deaths in the group operated upon after onset of labor. Of the 46 patients, 26 patients were from our own practice. Four of these were morbid, whereas nine of the 20 cases handled in consultation were morbid.

TABLE 1

Type of section	*Total cases*	*Morbid cases*	*Morbidity rate*
All types	190	36	19%
Elective sections	144	24	16
Low cervical section	77	11	14
Classical section	67	13	19
After onset of labor	46	12	26
Low cervical section	42	10	24
Classical section	4	2	

The extraperitoneal approach was used on six occasions. Three of these cases became transperitoneal by virtue of repeated perforations of the peritoneum. Three cases were successfully accomplished without trauma to the peritoneum. We feel this procedure today does not offer sufficient additional safety to the mother to warrant routine use in the parturient patient. The extraperitoneal approach may have a place in our armamentarium, but we believe it is highly selective. It would probably offer some additional protection in the grossly neglected and heavily infected patient or in the patient who has some other intra-abdominal condition in which it is desirable to avoid entering the peritoneal cavity.

In our series, hysterectomy following cesarean section was done four times, twice for incomplete rupture of the uterus, and twice because of repeated cesarean section scars. In no instance was the uterus removed as a precaution against infection. While our series of cases is small, we nevertheless are of the opinion that hysterectomy is not necessary in the management of potential or actual infection as has been recommended by Dieckmann.

The successful termination of pregnancy and labor is dependent upon several factors. The bony pelvis must be adequate for the particular child. The size of the fetal head must not exceed the allotable space in the maternal pelvis. This factor is further dependent upon the ability of the head to mold ade-

quately. The soft tissue of the pelvis must be nonresistant and, lastly, the contractility of the uterus must be sufficient to effect dilatation and expulsion of the fetus. It is quite obvious that one cannot accurately assess all factors prior to labor. We can obtain considerable information by physical examination of the unborn fetus and the maternal pelvis. X-ray mensuration of the bony pelvis will often offer valuable help in making decisions, but even this seeemingly accurate aid does not answer all questions, i. e., a pelvis with an interspinous diameter of 9.3 cm. might be adequate for a fetus of 2,500 gm., but would be of questionable adequacy for a fetus weighing 4,000 gm. One therefore cannot look at an x-ray plate or read an x-ray report and decide that the patient will deliver successfully. The decision must be made after evaluating all of the conditions present in each individual case. And so it is in the presentation of the material in this paper. It would be easier and probably more revealing to discuss in detail all the cases. Since this is not possible, we shall merely list the most demanding condition with the realization that it does not present the entire picture.

The indications for surgical intervention in our series of 46 parturient patients were varied (table 2). Any classification breaks down because of over-

TABLE 2

INDICATIONS FOR SECTION AFTER ONSET OF LABOR

		Total cases
I. POOR PROGRESS		23
Excessive size fetus (4,000 gm.)	8	
Occiput posterior	9	
Contracted pelvis	3	
Cervical dystocia	1	
Desultory labor only	8	
II. MAL-POSITION		8
Brow	3	
Deflexed head	3	
Transverse presentation	1	
Breech (primipara)	1	
III. FETAL DISTRESS		7
Prolonged labor	5	
Unexplained	2	
IV. MISCELLANEOUS		8
Previous cesarean section		
Unsatisfactory trial of labor	2	
Ruptured uterus	2	
Toxemia	1	
Placenta praevia	2	
Accidental labor in planned section	1	
Total cases		46

lapping circumstances. I have tried to separate the series into four large groups representing primary cause for intereference. The first and largest group consisted of cases in which labor and progress was proceeding at a very slow rate. The retarded progress may have been due to an excessive size fetus producing a true fetopelvic disproportion, or an excessive size fetus may have created an overly distended and inefficiently contracting uterus. The progress may have been retarded in part by the presence of the less favorable occiput posterior position. The slow labor may have been the result of a poorly functioning uterus without other unfavorable conditions, in other words, primary uterine inertia.

It is important to realize that the outline is a breakdown in which more than one abnormal condition may have occurred in the same case. In several cases, the progress was slow, but in addition to this, there was an oversize fetus in posterior position manifesting fetal distress. Eight cases were operated upon for slow progress associated only with ineffective pain. In this group the indication was primary uterine inertia. Many of these patients were handled before the introduction of intravenous pitocin. Since the use of this valuable drug, fewer cases have been handled surgically, and then only after the intravenous pitocin has proven ineffective.

The second group of patients was operated upon because the fetal position was believed unfavorable for spontaneous delivery. There were three primiparous patients in whom the fetal head was presenting as a brow and unengaged. All made very little progress after 24 or more hours of labor. Three cases were operated upon after full dilatation and failed forceps application. The fetus in each case was only slightly larger than average. The obstruction to labor was the loss of flexion of the fetal head, resulting in the unfavorable military position. All three of these cases had more than four hours of second stage without progress beyond the mid-pelvis. Each of these cases was later found by x-ray to have adequate pelves. One case of twin pregnancy was complicated by a double transverse presentation diagnosed soon after rupture of membranes and onset of labor.

There were seven cases operated primarily for fetal distress as evidenced by marked variation in the fetal heart. Here again classification is difficult because five cases were associated with prolonged labor. However, the primary reason for surgery was the apparent danger to the child. If no fetal distress had developed, the labor would have been allowed to proceed without interference.

The fourth group of patients was a miscellaneous series having various reasons for surgery, most of which require no particular emphasis. The two cases operated for ruptured uteri were to have had elective sections. Instead, labor began and was followed quickly by rupture of the old classical scar. Both cases were incompletely ruptured, allowing the delivery of living babies. Each case was subjected to hysterectomy.

The recommended lower uterine segment cesarean section is an easy operation to perform. It is surprising, however, to find that the classical section is still being done in a large percentage of cases in many hospitals.

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Rehabilitation of the Tuberculous*

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As applied to the physically and mentally disabled, "rehabilitation" means many, and often different things. Workers in the field are trying to find a better term. Most of us are agreed on the objectives—the restoration of the individual to the fullest physical, mental, social, vocational and economic usefulness of which he is capable.

Hardly a social or medical agency report or appeal for funds fails to stress its "rehabilitation services." Not that all are rationalizing or trying to cash in on the popularity of "rehabilitation," for considerably more is done now in the "enablement" of the handicapped, as our British friends have put it, than was done only five years ago.

Tuberculosis is a chronic, reactivating disease. We cannot build a rehabilitation program on clinical failure, nor does it avail to be vocationally successful and fail physically. Our primary concern should be to reduce relapses to a minimum, and to detect reactivation of the disease as early as possible.

We are equally concerned with moral deterioration. "Warming a steamer chair" for the rest of one's life may be worse than taking a chance at physical activity. Dr. F. W. Peabody commented in a statement published in 1950, "Death is not the worst thing in the world, and to help a man to a happy, useful career, may be of more service than the saving of a life."

Improved techniques in treatment have played an important part in assuring a greater chance of getting well. An understanding of the second phase of treatment, the after-sanatorium phase, has helped patients keep well and live useful, productive lives.

In-service training at the sanatorium, diversional, educational or prevocational, regulated activity to develop work tolerance, all play an important part in securing adequate stay as well as preparing the patient psychologically and physically for his readjustment to normal life.

Throughout this whole period the family must not be neglected, as it plays a vital role in the patient's adjustment to hospital treatment. It conditions the patient's cooperation from diagnosis to complete recovery.

The medical, social and, where necessary, psychiatric or economic care of the patient and his family, are essential services. To treat the individual and neglect the family is as unsound medically as it is socially. Early in our experiences we learned that the problems of each member of the family may exert a destructive influence on the patient because of emotional conflicts. Medical care for a sick wife or a child often accomplished what a reduction in hours at the workshop failed to do for a patient. The problem boy or girl, adjusted to the family, was more effective than extra diet or codliver oil.

We are concerned with the psychology of treatment. The Army Air Force made some conclusive demonstrations in early convalescence with diseases other than tuberculosis. A psychiatrist, discussing convalescence, stressed the harm done in keeping a patient unnecessarily in bed. The hospital official who explained to me that they keep patients at his hospital six to twelve months after arrest of their disease, to play safe, never heard the late Herman Biggs point out the danger of treatment that admits self-respecting sick men to the sanatorium, and turns out healthy loafers.

There is a marked difference in the attitude of patients treated at an institution with a well-regulated program of graduated activity, and those from a hospital with loose control, with no controlled activity, or perhaps an hour walking exercise before discharge. Whether the activity is therapeutic, educational, prevocational or avocational, these services turn out a patient better prepared for his readjustment. In the rehabilitation of the tuberculous we try to destroy the vicious circle of sickness, fear and insecurity. We are dealing with a complex situation in which medicine is interwoven with sociology, economics and psychology.

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There is a great value in the exploration and discussion of vocational objectives, particularly where the participants in the discussion include all the hospital services, medical, educational, social, and the agency that will help carry out the vocational objective. The plans then are not only more realistic, but hopefully will avoid an objective beyond the patient's potentials, which may result in waste and even contribute to a relapse.

The sanatorium services need not be at a vocational level to justify themselves. Those of us who get satisfaction in our jobs still feel the need of outside activities. How much more important this is when our job simply provides a living. With the tuberculous there is need, for a limited or indefinite period, of finding satisfaction at a slight physical demand level.

To provide gratifying hobbies may be most effective in preventing a breakdown. To oversimplify the problem of after-sanatorium care and permit the patient to believe that his only problem is his vocational training, is to invite danger. There is the readjustment to living in the family and the community, traveling in buses and subways in addition to school or work, as contrasted with the protective environment of a hospital.

In this post-sanatorium phase we are interested in retaining the gains made at the sanatorium and if possible, the return to gainful employment as early as his physical condition permits. The longer the period of hospitalization, and the more extensive the disease, the more difficult the readjustment. The socio-economic factors are important. Sir William Osler said: "Tuberculosis is a social problem with a medical aspect."

With a reactivating disease the effectiveness of treatment may be measured in years of useful, productive life. Have we made as much progress in preserving the improved status as we have in the treatment of the disease? How many institutions know what happens to their patients the first five years following treatment? Those years following sanatorium treatment are hazardous years.

While attending an international conference on after-care at Cambridge, England, I learned of two studies of patients followed up for five years after discharge from the sanatorium, closed as inactive and picked up again several years later. The Lancashire County Council in a study of 4,231 such cases found that only 3.8 per cent of these recovered cases had renewed activity. In a series of 2,488 similar cases in the London County Council Area the number reached 3.9 per cent.

For a substantial number of patients there is a dangerous gap between the protected environment of the hospital and the impact of everyday life. As one doctor put it "For many patients correct assessment requires not only clinical intuition, but the application of certain tests and watching under actual working conditions which are far removed from what comes under the term of occupational therapy."

The fifth report of the employment committee of the joint tuberculosis council in England discussing work capacity, states: "Much has been written about tests—psychological, physiological, intelligence and others, which will enable administrators and clinicians better to understand and appreciate the capabilities of tuberculous patients, but experience in the administration of rehabilitation schemes tends to show that there is no substitute for periods of observation on the clinical, technical and temperamental qualifications of a candidate."

To this we would add observation during exposure to actual living and traveling conditions that are part of life at home and in the community. The social and economic, as well as the emotional factors in adjustment, are often as important as physical care. All should be considered in any plan for treatment and rehabilitation.

Dr. R. B. Lewis of St. Marks College, University of Adelaide, presented statistics in the Medical Journal of Australia, in 1950, supporting the belief of many medical men that although the death rate from tuberculosis has fallen considerably, the outlook for the individual is no better than it was 30 years ago. We know this need not be so.

Dr. H. H. de Boer writes in Vocational Rehabilitation of the Tuberculous published in 1950 by the International Labour Office, "It is in the greater proneness to relapse that the physical status of the arrested tuberculous differs considerably from that of the majority of the disabled persons. Experience has shown that rehabilitation shortens the period of incapacity and reduces the degree of invalidity, thereby diminishing the cost of invalidity, pensions and social assistance, whether from public or private sources."

In getting well we have made considerable progress, not so in staying well, or the return to a job. A large percentage of relapses is not so much the fault of the sanatorium as of the

community which fails to recognize that after-care for many patients is a necessary part of the care of the tuberculous.

In the January 1952 Bulletin of the National Tuberculosis Association, Dr. Raymond C. McKay, in an article entitled "The Past Two Decades in Tuberculosis Treatment," says "Over twenty years' retrospect shows that the obligation to cure has been well and faithfully discharged, but we can take little pride of achievement in the field of rehabilitation and isolation. The incidence of relapse and of unauthorized discharge remains high. Without far greater progress in the next two decades than we have witnessed in the two just completed, our record with respect to these functions will still be labeled 'failure' when we gather to celebrate the final conquest of tuberculosis."

Public concern with this important problem, which is based on dissatisfaction with the experience of patients after graduating from sanatoria, is not limited to the United States and Canada. Many of our friends in England are agreed that the provisions for after-sanatorium care have not found their proper place in the antituberculosis program.

Desire or habit to serve someone, to work, has been the pattern of our lives, and usually the happy part of our lives. Unless we provide some opportunities for work for those who can work, we must put the disabled on permanent relief, with the demoralization, dissatisfaction and discontent that inevitably follow. With the tuberculous it means getting people well through expensive treatment, but through idleness, creating new problems that invite relapse with further hospitalization. For a large number of patients there will continue to be a dangerous gap between discharge from sanatoria and full time work in indusrty.

No matter how adequate the facilities for hardening, it is necessary to educate employers to an understanding of the employability of properly conditioned patients. There has been marked improvement in employment opportunities for the tuberculous since I reported in 1938 on industry's practice in the employment of the tuberculous. However, too many prejudices still exist and a worker with a history of apparently arrested tuberculosis, is too often turned down even if otherwise qualified.

The extreme, found on inquiry, was a very large corporation whose head of personnel advised me that they never accepted a worker with tuberculosis though I knew the chairman of the board of directors had been treated at Colorado Springs thirty years before. Often the excuse was that insurance carriers opposed employment of the tuberculous. Some of the largest insurance companies not only denied this, but one told of a successful experience in re-employing patients over a period of twenty years.

Few employers in New York know of our second injury provision which protects against complete responsibility in the event of a breakdown which may become compensable.

It was found that the seniority rules of labor unions often operated against the best interest of some patients. With a railroad, as well as a large rubber company, transfer to a new job and a new union within the same organization means loss of seniority. The patient employed as a boilermaker with a railroad company for twenty years, after the arrest of his disease, preferred returning to his old work against medical advice and suffered a breakdown.

A U. S. Department of Labor publication (August 1952) stated that a union in Rochester, New York, negotiated a contract "which gives three years seniority to handicapped workers the moment their probationary period expires. They hold this until their accumulated seniority exceeds three years. The handicapped worker is thus given much advantage over able-bodied employees. The clause, initiated by the union, was gladly accepted by the company, according to the A.F.L. Weekly News Service."

Sheltered workshops and colonies have shown that relapses can be reduced, and many patients in all stages of the disease gradually returned to partial or complete selfsupport. They have served as demonstration centers for industry. Productive work under medical supervision does more than reduce relapse. It is a constructive preparation for the life to which the patient must return. It is a form of self-help in which the patient takes a necessary share of the responsibility for his support and that of his family. Any activity which is economically useful provides a satisfaction—a sense of real living—of earning one's keep.

Most patients make a sufficient recovery at the sanatorium to return to a selected job, or to school, college or vocational school. A substantial number require industrial convalescence, a period of hardening through graduated work under medical supervision, before they are ready for school or a job. Reducing the physical and mental hazards to a minimum, there is every possibility that, properly prepared, they will negotiate the training or the job without relapse. Tuberculosis is a relapsing disease, and it is

more important to be well and working five and ten years after treatment, even if employment is temporarily deferred. To spend six months resting at home after discharge from a veteran or civilian hospital, condition arrested, is demoralizing physically and mentally. Some persons select educational courses after discharge to put off facing the realities of normal living.

For several years we have advocated earlier discharge of cooperative sanatorium patients. Psychiatrists have pointed out the danger of keeping persons in a hospital bed or in a medical institution, longer than necessary. With a long drawn out disease like tuberculosis, this has social as well as medical and psychological implications.

Those whose tuberculosis has been stabilized could be graduated to a sheltered workshop with its carefully regulated program of work and rest, when they reach three hours activity. Restored to their homes from two to twelve months earlier than is customary, such a program would have medical, social and economic values for the patient, his family and the community. It should result in earlier rehabilitation, fewer relapses, and increased facilities for the acutely ill without additional capital or maintenance costs.

For those who require temporary sheltered employment, this may be secured in industry, and to such extent as work or conditions are not suitable or available, in philanthropic sheltered workshops. Sanatoria often provide sheltered employment. For those who require such employment permanently, this will, with few exceptions, be available only in institutions, colonies or sheltered workshops.

Utilizing graduated work with medical and social care and supervision, sheltered workshops have as their objectives, the physical, psychological and social adjustment of the patient. They are concerned primarily with preventing relapses. It is a scheme of hardening through productive work, where the hazard of a breakdown is greatly reduced and the psychological value of earning on a competitive basis is retained. Simulating industry in equipment and methods, it provides work and rest under careful medical supervision. While it sells competitively and pays prevailing or union rates for work produced, it sacrifices economy in production for safety of its patients. It carries a person from three hours work tolerance through graduated work to a full day. For some it provides hardening up to the time when they may safely start on a vocational training program and, when the training is complete, be ready for employment in industry.

Dr. Norvin Kiefer, in his book on tuberculosis, states that a suitable avocation, especially for young patients, is of great importance. There is a tendency in practice, he says, to think first of a new occupation although many physicians point out advantages of returning to the old job if there are no contraindications.

The personality factors, he believes, often are more important than aptitude tests, and he reminds us that our primary concern should be conditions that will reduce the hazards of relapse. Salmon is quoted: "The inherently inept handicapped person like the inept able-bodied person, might far better be made versatile at a lower occupational level where he can adapt himself to the stresses and strains of economic changes, than to be placed in a position where he is made to compete at a highly skilled level with capable, able-bodied and the adept handicapped."

A psychiatrist is quoted as urging that vocational rehabilitation with the tuberculous should be delayed until the patient is physically and emotionally secure.

The Altro Work Shops, started in June 1915, grew out of a study of graduates of sanatoria which disclosed that of the patients discharged as improved, quiescent or arrested, 50 per cent were worse or had died within six to eighteen months after discharge. In a clinical study of the first twenty-five years, Dr. Louis E. Siltzbach of our staff found that 10.3 per cent of Altro patients had died within the first five years after discharge from the workshop. Of those who were graduated from the workshop, less than 3 per cent died within that period.

In addition to serving tuberculous men and women, Altro has been providing rehabilitation services for cardiacs since February 1948. While the number served during the first four years, 108, is small, we believe that the experiences have been significant.

During the last thirty years Altro has served an increasing number of moderately and far advanced cases of tuberculosis—some good chronics who, after treatment, still have occasional positive sputum. Socially as well as physically, some of the most satisfactory experiences have been with these good chronics. You can find them in every civilian or veteran hospital, or at home prematurely condemned to the scrap heap.

On the 35th anniversary of Altro Work Shops the story was told of our former designer, a tuberculous "good chronic" who, admitted to

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Thirty-two Cases of Renal Glycosuria*

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This is a report of 38 cases of persistent nondiabetic glycosuria found during the routine examination of 19,358 young adults. In reviewing the literature of glycosuria which is neither caused by diabetes nor is of the transient normal variety, one comes across several possibilities of glycosuric melitura. (1) There is a true renal glycosuria in which it is defined as having a fasting blood sugar below 100, with a normal or flat glucose tolerance curve, and with glucose found in every urine specimen (even the fasting). (2) Pseudo-renal glycosuria which is believed not to be uncommon as contrasted with renal glycosuria, in which it is stated that as the blood glucose level diminishes toward 100 mg., the glycosuria diminishes, and under fasting circumstances completely disappears. The glucose tolerance curve is normal. The utilization appears to be normal. It was also stated that there is an increased incidence of diabetes developing late in this syndrome. (3) Elementary glycosuria which is employed to designate urinary excretion of glucose by certain apparently normal individuals after the ingestion of large quantities of cane sugar, glucose, starch, and the like. (4) Transient hyperglycemic nondiabetic glycosuria in which the blood sugar level may get above 150 and as a result there will be sugar in the urine. (5) In addition there are those other sugars which cause meliturias, such as pentose, fructose, galactose, maltose, sucrose, and lectose.

REPORT OF 38 CASES

In reporting the 38 cases noted at the University of Minnesota we have gone into the early findings, history, and laboratory procedures in some detail and find that out of 19,358 physical examinations there were 155 glycosurics of which 38 were considered to be of renal type. The people examined were in the age span of 14 to 40 with a concentration at 17 to 27 as students of the University of Minnesota. The oldest patient showing this type of finding was 37; the youngest was 17. The routine consisted of calling back all those individuals who had glycosuria on the examination, repeating this study, taking a full and complete history, and having a glucose tolerance curve of the two and one-half hour type with 100 grams of glucose being given. These patients were examined from 1948 to 1952 with the opportunity of followup in some instances being over six years. The terminology as suggested above from the literature gives rise to considerable conjecture, particularly with regard to pseudo-renal glycosuria. We have been unable to find sufficient statistical followup on particular glucose curves to indicate that the pseudo-renal glycosuria has the predilection for diabetes mellitus that has been assigned it. Of the 38 cases examined, 32 had fasting blood sugars which were normal (below 100), with normal curves and with transient urinary sugar (figure 1). Six had a normal fasting blood sugar but with an abnormally high peak curve, although with a return to normal and with a transient glycosuria. Thus there were

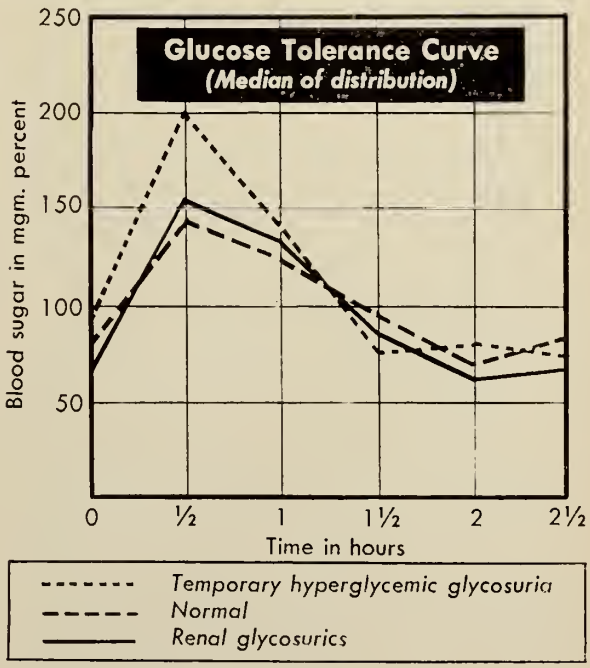

Fig. 1. Glucose tolerance curve.

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TABLE 1

TOTAL EXAMINED = 19,358

	Total cases	*Cases 10,000*	*Male*	*Female*
Diabetics	70	36	48	22
Renal glycosurics	32	16	30	2
Temporary hyperglycemia glycosuria	6	3	6	0
Normal	47	24	39	8
Total cases	155	80	123	32

16 cases per 10,000 of the so-called pseudo-renal glycosuria and three per 10,000 of the possible latent type diabetes mellitus. Of the pseudo-renal glycosurics 30 were male and two were female. Of the latter there were six male and none female (table 1). The family history showed that there were eight patients who had a history of having diabetes on one side of the family, 21 with none, and three had a history of renal type glycosuria. These all were in one family. Of the six with the high curve, two had a history on one side of diabetes, four had no history whatsoever (table 2). The weight of 34 of the 38 was normal or underweight, with

TABLE 2

	FAMILY HISTORY DIABETES		FAMILY HISTORY RENAL GLYCOSURIA	
Diabetes	28	5	37	1
Renal glycosurics	8	0	21	3
Temporary hyperglycemic glycosuria	2	0	4	0
Normal	10	0	37	0

four being overweight (table 3). The blood pressure readings were normal (table 4). Patients were checked for the other sugars such as pentose and fructose when indicated. We found none. The fasting blood sugar in the group of 32 had a range of 72 to 100 mg. per cent with an average of 81, in the group of the high curve from 84 to 102 with an average of 90. It may be noted that the normal group found during the study had a range from 69 to 105 (table 5). In addition to the 38 people that we have been citing, we have had the opportunity of following three male faculty members, who have been under the care of the Health Service of the University of Minnesota for a period of years. One had been followed for 15 years. Of the three, two have normal fasting blood sugars, with a high peak up to about 200 mg. per cent within an hour and returning to normal within an hour and a half to two hours.

TABLE 3

WEIGHT

	Normal		*Underweight*		*Overweight*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Diabetics	17	6	28	2	3	14
Renal glycosurics	16	1	11	1	3	0
Temporary hyperglycemic glycosuria	4	0	1	0	1	0
Normal	22	3	13	1	4	4

TABLE 4

BLOOD PRESSURE

	Range	*Average*	*No. abnormal*
Diabetics	116/64–146/98	122/78	2
Renal glycosurics	108/60–142/90	118/70	1
Temporary hyperglycemic glycosuria	104/62–128/78	120/72	0
Normal	100/64–132/80	116/72	0

TABLE 5

FASTING BLOOD SUGAR

	Range	*Average*	*Median*
Diabetics	High	High	High
Renal glycosurics	72–100	81	80
Temporary hyperglycemic glycosuria	84–102	90	86
Normal	69–105	84	80

During this period there was transient glycosuria. Each of these men has been followed by different observers over a period of years and repeated glucose tolerance curves have been done. In none of the three instances has the curve altered to the point of further suggesting diabetes. One individual, who is 62 years of age, remembers having been told of sugar in his urine 22 years ago.

A definite number, about one third, of these 38 individuals have rebound hypoglycemia, if permitted to go about three hours after the ingestion of glucose. Of the entire group of 38 plus the three faculty members that have been cited above, we have had an opportunity of following them all regularly with no change whatsoever to date. The only change noted in the study was that of one male, whose fasting sugar was normal (110 mg. per cent). The curve went to a peak of 200, but the return within two and one-half hours was only to 130 mg. per cent. This did not drop further in the prolonged test. A subsequent glucose tolerance test six months later showed a normal fasting sugar (112) with a peak to 200. On this occasion the drop was to but 150 mg. per cent in two and one-half hours. This person had no symptoms, but is being followed as a minimal diabetic and is not

included in the group cited. The period of followup is as little as one year, and as many as 15, but with an average of about three. It has been our policy to repeat the glucose tolerance curve yearly and to compare them with the original determinations. It is our hope that over the period of the next several years we will be able to follow closely those individuals who were included in this group.

I feel it is not entirely true that renal glycosurics necessarily have sugar in their urine at all times (including fasting). The statement also that those individuals who have the same glucose tolerance curve and findings, but who have no glycosuria on fasting should be called pseudo-renal glycosuria and have a greater chance of developing clinical diabetes mellitus is not convincing. We could find no evidence in the literature of a controlled study of normals and renal glycosurics over a period of years in which diabetes was found more prevalent. Therefore, it is our belief that the diagnosis of renal glycosuria can be given to any individual who has a normal curve, but who has glycosuria at some time during the glucose tolerance test. Certainly the explanation cannot be in the glandular response when the blood glucose response is the same as normal. Rather it must be in the excretory system and therefore is renal in nature. Also, we have chosen to call that group with a high peaked curve, but with a return to normal, temporary hyperglycemic glycosuria. These we feel warrant close observation although apparently having a slow but adequate insulin response.

As a result of our study of glycosurics and our following of the individuals with diabetes, we have come across three cases of glycosuria, which were not diabetic in nature, but rather were renal type, and who have been receiving insulin. It is well known, but worth repeating, that one cannot make a diagnosis of diabetes on the basis of a positive sugar test in the urine. It had been remarked that high sugar, three to four plus in the urine, would certainly suggest diabetes mellitus. However in our series of 38, the average was one to two plus but there were 15 per cent who had three to four plus sugar in the urine at some time. The first of the three individuals whom we saw was a graduate student from South America who had a diagnosis of diabetes made there without any blood sugars having been determined. He was placed on insulin. He then went to another university in the United States where he stated that he had diabetes and gave them his insulin dosage. He was continued on this dosage but inasmuch as he had some reactions, the amount was diminished. Shortly thereafter he came to the University of Minnesota where again he stated that he had diabetes and that he was on 30 units of protamine zinc insulin. (Incidentally, he was started on 40 units of protamine zinc.) In view of the fact that he had many reactions, never had sugar in his urine even after meals, and that he had not had a fasting blood sugar, we gradually cut down his insulin dosage, finally took it away from him entirely, and then did a glucose tolerance test which showed him to have a normal curve with glycosuria evident.

Another instance was that of an 18-year-old boy who stated that he had diabetes and was taking insulin. However, there was no sugar in his urine and, in further discussion with him, it was determined that he had never had blood sugar studies. He was taking 20 units of regular insulin and 20 units of protamine zinc insulin at that time. We gradually cut his insulin dosage and finally obtained a glucose tolerance curve after a period of several weeks without insulin. This curve proved to be perfectly normal with no evidence of glycosuria whatsoever. It may be noted here, too, that he had had several reactions.

The last was a 17-year-old girl who for three years had been receiving insulin in the dosage of ten units of protamine zinc insulin because of sugar in her urine. Here too, because we had been alerted by the South American, we cut down her insulin, checked her urinalyses and finally obtained a glucose tolerance curve which also was normal in nature. In all three instances, the glucose tolerance curve was repeated after several months of no restriction with no change being evident.

SUMMARY

Thirty-eight cases of persistent recurrent glycosuria on a non-diabetic basis found in 19,358 patients examined are presented. The family history of diabetes is less than in diabetics. There is no tendency to obesity. The blood pressure range is normal. Fasting blood sugars were within normal range.

The glucose tolerance curves fell into two types: (1) The normal curve with the peak generally being under 150, but with sugar in the urine; (2) A high peak curve, with the upper reading over 180 and in some instances over 200.

There was a return to normal or hypoglycemic state within two and one-half hours, and glycosuria occurred. The instances of three individuals receiving insulin therapy without having had a diagnosis of diabetes mellitus by glucose tolerance curve is described.

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Clinical Evaluation of Elkosin in Refractory Genito-urinary Tract Infections*

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ELKOSIN is a sulfonamide which has been extensively used in Europe for more than a decade because of its wide range of antibacterial activity, low incidence of toxic reactions, convenience of administration and low cost.[1] It is easily soluble, readily absorbed from the gastrointestinal tract, rapidly diffuses into all body fluids, and is excreted by the kidneys in high concentration with minimal acetylation and crystallization.[2]

This study was undertaken to determine toxicity and possible value of Elkosin† in patients with genito-urinary tract infections that had recurred after or were refractory to other antibiotic treatment. Toxic reactions were minimal and broad antibacterial activity was confirmed.

METHODS

In a large general hospital such as that of Los Angeles County, there is constant turnover of patients with chronic urinary tract infections which are usually resistant to medication. The diabetic wards and the "G-U" clinic were the chief source of clinical material. Urine for examination was collected by catheter from females and by a "clean" technique from males. Bacterial cultures were carried out by the laboratories of the Los Angeles County General Hospital. Blood sulfonamide levels were done by a variation of the Bratton and Marshall method. Routine blood and urine counts and stains were done on fresh specimens. "In-patients" were usually observed every day and "out-patients" at weekly intervals. A standard oral dose of 1.0 gram of the sulfonamide three times a day after meals and at bedtime was prescribed. This dose was given until 50.0 grams had been taken.

CLINICAL DATA

Of the 56 adult patients treated with Elkosin, 25 were female and 31 were male. Twenty-four were studied on a diabetic ward. These patients had pyuria and genito-urinary infections incidental to the complaint for which they were hospitalized. Twenty-four were ambulatory males with chronic genito-urinary infections. The other eight had miscellaneous primary diagnoses with secondary urinary tract infections.

All of the patients had been treated at one time or another with other sulfonamides or antibiotics. At the time the sulfonamide Elkosin was given, the clinical evidences of infection were mild dysuria, nocturia, pyuria and bacilluria. The clinical responses as judged by improvement in these findings are presented in table I.

TABLE I
CLINICAL RESPONSE TO SULFONAMIDE

Degree of response	*Number of patients*
Good	21
Moderate	5
Slight	2
None	23
Inadequate data	5

Table II presents sulfonamide levels found in 10 consecutive patients who responded well to the medication compared to those levels found in 10 consecutive patients with no clinical response. It is evident that the blood level of sulfonamide had no direct bearing on the clinical response.

TABLE II
SULFONAMIDE LEVELS IN BLOOD DURING TREATMENT

Good clinical response mg./100 ml.	*No clinical response mg./100 ml.*
4.95	4.78
1.97	1.6
1.25	2.34
3.58	2.08
2.33	3.17
1.88	5.63
4.0	2.94
5.65	4.31
3.83	3.72
1.17	0.74

*From the Department of Medicine, University of Southern California school of medicine, and the Los Angeles County General Hospital. This work was supported in part by a grant from Ciba Pharmaceutical Products.

† Tradename for N'-(2,6-Dimethyl-4-Pyrimidyl)-Sulfanilamide.

Negative gram stains of urine sediment and/or negative urine cultures occurred after treatment in six patients. Absence of the original predominant organism after treatment occurred in 14. Diminution of bacilluria was evident in the remaining patients. No studies of bacterial resistance were done.

TABLE III

Infectious organisms	*Disappeared during treatment*	*Continued during treatment*
E. coli (19)	2	8
Alpha streptococcus (1)		1
Pseudomonas (3)	1	2
Beta streptococcus (2)	1	1
Staphylococcus albus (1)		1
Aerobacter aerogenes (7)	5	2
Staphylococcus aureus (3)	3	
Shigella dispar (1)	1	

The disparities in the tabulation (table III) of infecting organisms result from multiple infections and incomplete data in some cases.

Medication was stopped in two patients because of nausea and in one patient because of a drop in white blood count from 6,750 to 3,550 per cu. ml. during one week. No hematuria, skin rashes nor other toxic manifestations were observed.

DISCUSSION

Sulfonamides are active antagonists to many gram-negative and gram-positive bacteria. The newer sulfonamides, as typified by sulfadiazine, are considered the drug of first choice in certain diseases such as meningococcemia with or without meningitis, cholera, trachoma, chancroid and lymphogranuloma venereum. At present the popularity of the new sulfonamides for general use is on the increase. This swing of the popularity pendulum is most likely motivated by the occurrence of unpleasant side effects from the indiscriminate use of penicillin and other antibiotics.

The ultimate usefulness of Elkosin will depend on much larger scale studies than those presented here. The vast European experience suggests that a clinical evaluation in direct comparison to penicillin, streptomycin, aureomycin, terramycin, and chloramphenicol for the treatment of commonplace infections would be worthwhile especially in view of convenience and economy of the sulfonamide if proven efficacious and safe.

CONCLUSIONS

This clinical study demonstrates that this sulfonamide Elkosin is a safe and effective antibacterial agent. Its usefulness in recurrent and refractory genito-urinary tract infections is limited by the sensitivity of the infecting organisms. If sensitivity studies are practically available, Elkosin should be included as one of the potential therapeutic agents.

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CESAREAN SECTION AFTER ONSET OF LABOR

(Continued from page 270

TECHNIQUE

Since this situation prevails, it is well to very briefly mention the technique. The sections are done under local infiltration and block anesthesia, using 1 per cent procaine with 5 minims of adrenalin in each 100 cc. The uterus is opened through a transverse incision in the lower uterine segment after superior and inferior peritoneal flaps have been created about one inch below the pectineal line. The incision through the musculature may be made with bandage scissors or the opening can be created by placing fingers in an initial perforation, spreading and tearing the tissue laterally. The uterine wall is closed with a row of interrupted catgut and a row of continuous catgut. The superior peritoneal flap is sutured to the uterine musculature below the level of the incision. The inferior flap is drawn upward and sutured to the anterior uterine wall at the junction of the corpus and lower segment. This creates a double layer of peritoneum over the uterine incision. The abdomen is closed without drainage, even in the grossly contaminated cases. Up to the present time, no intra-abdominal antibiotics have been employed.

SUMMARY

The purpose of this paper has been the presentation of our experiences in the use of the lower uterine segment section after onset of labor. It is felt that the results justify the use of the lower uterine segment cesarean section for potentially and actually infected parturient patients. The indications for interfering with labor have been listed. It is our opinion that the use of antibiotics, chemotherapy, transfusions, and improved operative technique has widened the indications for surgical delivery.

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Track Stars Are Not Barrel Chested*

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THE CORRELATION between thoracic contour and health or tuberculosis has interested me for many years. From 1926 to 1939 an extensive survey on the development of the chest was made.[1] Over 20,000 chests were measured, including all age groups as well as healthy and tuberculous individuals. The following conclusions were reached on the basis of this study:

1. At birth an infant's chest is practically round. Normally, by the age of one year, the chest has flattened so that the average depth is 78 per cent[2] of the average width (a thoracic index of 780); and by the age of five years the average thoracic index is 720. The decrease in thoracic index continues as the child matures; and by puberty the average healthy boy or girl has a thoracic index of 667, a fully developed chest (figure 2).

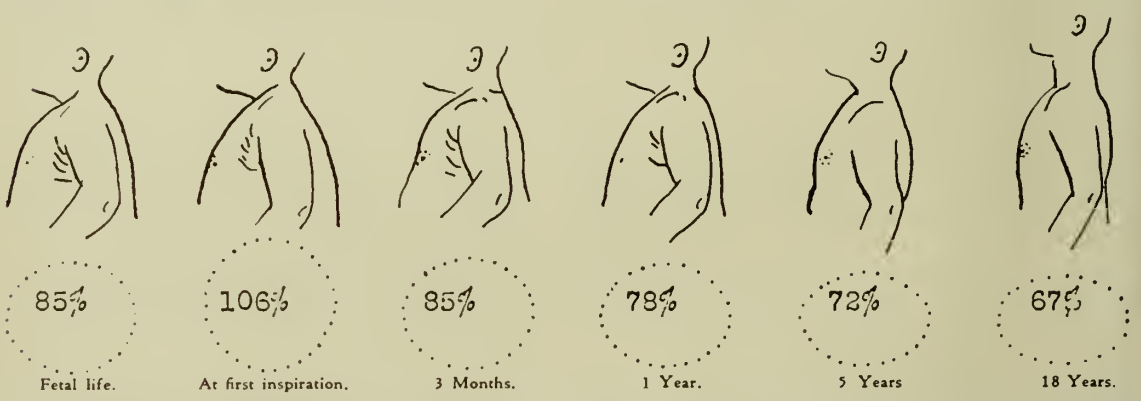

Fig. 2. Diagrammatic sketches showing changes in chest contour from fetal life through adult age. (*Your Chest Should Be Flat*, S. A. Weisman, M.D., J. B. Lippincott Co., Philadelphia, 1938.) Note that there is only 5 per cent difference in the chest contour between the ages of 5 and 18.

2. The average thoracic index of individuals with pulmonary tuberculosis was found to be 770, the tuberculous chest being narrower and deeper than the normal adult chest (figure 1).

3. The aevrage thoracic index in a large group of children in poor socio-economic strata was greater than that of a similar group of a more favorably endowed level. It was also found that in two groups most distantly separated economically the incidence of positive tuberculin reactions was ten times as great in the poorer group.

4. Since the thoracic indices of adults with pulmonary tuberculosis and of children with positive tuberculin reactions were so similar to those of infants of one year of age it was concluded that the tuberculous chest was retarded in its early development and was an infantile type of chest. (This agreed with the earlier conclusions of Hutchinson.[3])

Frequent references by some sport writers to certain great track stars as being "barrel chested" and "deep chested" led me, in 1940, to measure a number of stars who participated in the National Collegiate Athletic Association track and field meet held in Minneapolis, Minnesota.[4] Ninety-eight chests were measured. The results of that limited study, as shown in table 1, were as follows:

1. The mean thoracic index for the entire group was 677 (67.7 per cent).

2. Men participating in track events had a slightly flatter chest than those participating in field events.

3. With few exceptions track stars have flat, wide chests.

In June 1949 the National Collegiate track and field meet was held in Los Angeles. Again measurements were made of participating athletes to reaffirm the findings of the study of 1940.

PROCEDURE

One hundred and twenty participants were measured for height, weight, width and depth of chest (at nipple line), and width of pelvis

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(at anterior superior spine). (See tables 2,A, B,C,D.)

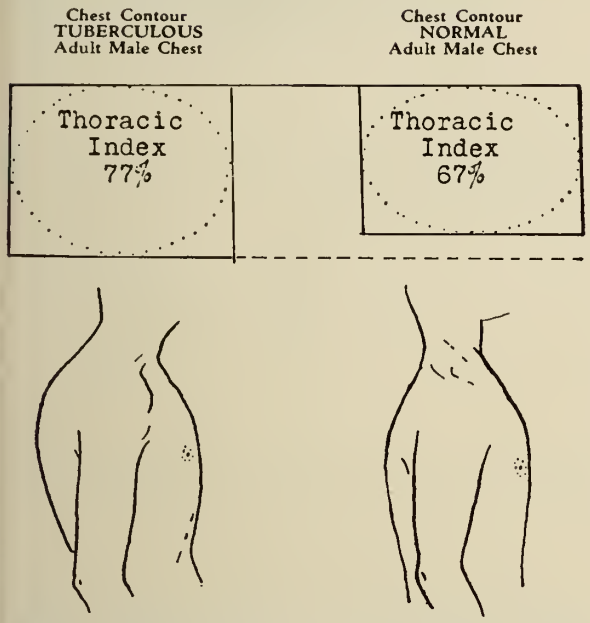

Fig. 1. Diagram of cross-sections of tuberculous and normal chests. (*Your Chest Should Be Flat*, S. A. Weisman, M.D., J. B. Lippincott Co., Philadelphia, 1938.)

TABLE I

MINNEAPOLIS MEET (1940)
MEAN THORACIC INDEX IN GROUPS

Event	*Mean thoracic index*	*Number of cases*
440 yard dash	654	11
Pole vault	660	6
Broad jump	661	5
High jump	667	7
100-200 yard dash	667	13
Two mile run	678	4
Hurdlers	679	17
880 yard dash	688	14
Discus	689	6
Javelin	696	9
Shot put	700	6
		98

Mean thoracic index for 98 cases = 677.
72.5% had a thoracic index not over 700.
94.9% had a thoracic index below 750
Only 5.1% had a thoracic index of 750 and over.

TABLE II

LOS ANGELES MEET (1949)
(A)

Event	*Mean thoracic index (T.I.)°*	*Number of cases*
100-220 yards	661	17
Hurdlers	661	15
440-880 yards	664	28
High and broad jump	667	7
Pole vault	667	5
Javelin	672	6
One to two mile	682	25
Shot put and discus	687	17

Mean thoracic index for entire group = 667.
In 77% the T.I. was not over 700.
In 94.2% the T.I. was less than 750.
In 5.8% the T.I. was 750 and over.
°Ratio of depth of chest to width.

(B)

Event	*Mean iliac-tr. chest index (I.C.)°*
Hurdlers	1038
Javelin	1027
One to two mile	1019
440-880 yards	1013
100-220 yards	1007
Pole vault	983
Shot put and discus	968
High and broad jump	964

°Ratio of width of pelvis (ant. sup. spine) to width of chest (at nipple line).

(C)

Event	*Mean height (inches)*
Shot put and discus	75
Javelin	73
Hurdlers	72
High and broad jump	72
Pole vault	72
100-220 yards	71
440-880 yards	71
One to two mile	70

(D)

Event	*Mean weight (pounds)*
Shot put and discus	220
Javelin	176½
High and broad jump	170
Hurdlers	166
Pole vault	165
100-220 yards	158½
440-880 yards	155
One to two mile.	147

RESULTS

The mean thoracic index in the 1949 group was found to be slightly less, indicating a slightly flatter chest, than the mean thoracic index found in the 1940 group; 667 or 66.7 per cent (Table 2A).

The track men, again as in the 1940 event, appear to have slightly flatter chests than those participating in the field events.

The shot put and discus group in the Los Angeles meet, as the shot put and discus group in the Minneapolis group, had the deepest chest of all the groups participating.

The tallest and heaviest in general were the shot put and discus throwers.

The shortest and lightest in general were the one and two milers (table 2, C and D).

Comparisons were made on the ratio of the width of the pelvis to the width of the chest* It was found that the iliac-transverse chest index was greater in the track men, particularly in the hurdlers, than in those participating in the field events (table 2B).

The shot putters and discus throwers had the narrowest hips (table 2B).

In other words track men, on the average, appear to have flatter chests and wider hips than athletes carrying on in field events (figure 3).

Shot putters and discus throwers are the deepest chested of all the groups. However, shot putters and discus throwers cannot be called deep or barrel chested since the average depth of their chests is only slightly greater than the

°Iliac-Tr. Chest Index (I.C.) = Ratio of width of pelvis to width of chest.

Fig. 3A. Mean thoracic contour of the entire group.

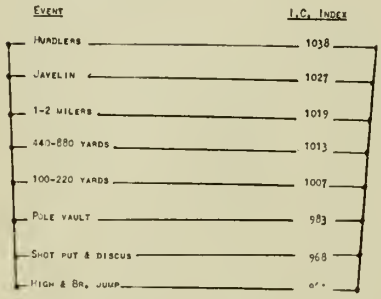

Fig. 3B. Mean ratio of width of pelvis to width of chest in each event (I.C. Index).

depth of a perfectly normal chest which is flat and wide.

THORACIC CONTOUR AND HEART SIZE

Whether or not a relationship exists between thoracic contour and cardiac size is of interest. Such a study is now being conducted. In general the individual with a flat broad chest has a broad, transverse heart – the individual with a deep narrow chest a long, narrow heart. To determine cardiac size fairly accurately one may employ the ratio between the frontal cardiac silhouette and the height and weight of the subject.[5–9] Such statistics indicate that the transverse, broad heart is of greater size than the long, narrow heart in subjects with similar height and weight but with dissimilar thoracic indices.

Whether variations in cardiac size partially determine physical speed or whether speed and endurance partially determine cardiac size is also of interest. In various mammals there seems to be some relationship. The cardiac size in relation to body weight is greater in the hare than in the wild rabbit; the heart of a deer is half again as large as that of a dog when similarly measured.[10] These observations in animals may be applicable to man and may partially explain the greater proficiency in sprint events of the shorter, lighter weight track stars as contrasted

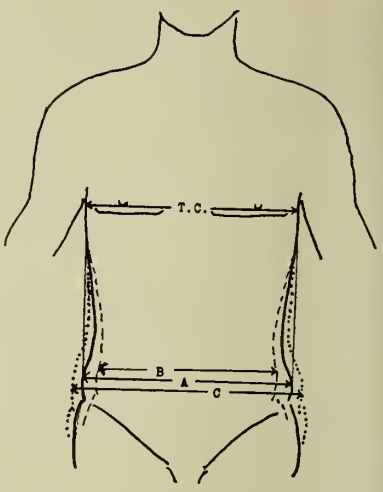

Fig. 4. Schematic drawing showing relationship of transverse chest–transverse pelvis in field and track stars.
T.C.=Transverse chest (at nipple line)
ABC=Transverse pelvis (ant. sup. spine)
A=Sprinters
B=Shot put and discus throwers
C=Hurdlers

with the brawn without speed of the taller and heavier participants in field events.

CONCLUSIONS

1. Measurements on the shape of the chest made on a group of athletes participating in the 1949 National Collegiate track and field meet held in Los Angeles tend to corroborate the measurements made on a similar group of athletes participating in the 1940 National Collegiate Athletic Association track meet held in Minneapolis, Minnesota.

2. Chest measurements indicate that track stars are flat and wide chested and not deep or barrel chested as they have frequently been called.

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Section on PAIN

THE JOURNAL-LANCET *feels sufficiently encouraged with the response to the Section on Pain so that tentatively it has been agreed that the Section on Pain will appear at the beginning of each quarter – January, April, July and October. The present intention is to feature material that emphasizes the element of pain wherever it manifests itself in connection with the patient's condition. Articles conforming to this idea will be welcome for consideration to be included if possible in the material appearing in the Section on Pain of* THE JOURNAL-LANCET.

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Cordotomy in the High Cervical Region for Intractable Pain

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THIS REPORT concerns the surgical relief of intractable pain arising in the region of the brachial plexus, the arm, the chest, or the upper abdomen. Effective means of relieving pain in these areas has not until recently been available. The pain usually is secondary to cancer. Less frequent causes are tabetic crises, phantom limb, radiation and traumatic neuritis, arthritis, and herpes zoster. Obviously pain from functional causes must be excluded. The operation consists of sectioning in the region of the second cervical vertebra, the spinal cord tract carrying pain and temperature sensation, i. e., the lateral spinothalamic tract. Data obtained from a series of 42 patients who have undergone such operations are the basis of this report.

ANATOMY OF PAIN-CONDUCTING FIBERS

An understanding of the anatomy of pain-conducting fibers is necessary to appreciate the advantages and limitations of cordotomy. Obviously interruption of specific pain-conducting axons within the spinal cord must, to obtain permanent pain relief, include all such axons. There should be no "islands" of pain sensation remaining. Likewise the level of analgesia must be well above the site of entrance into the cord of the pain-conducting axons. To help recall the anatomy of these tracts, the following data are presented. Painful impulses arise at naked nerve terminals which are specific for that sensation, and are scattered throughout the skin, subcutaneous structures, and viscera. The impulses are carried through myelinated or non-myelinated fibers either (1) directly through somatic nerves to the posterior root ganglia (somatic afferent fibers) or (2) indirectly in sympathetic nerve trunks, through the sympathetic ganglia, then via the white rami communicantes to the posterior root ganglia (visceral afferent fibers). The cell bodies of all sensory nerves lie in the posterior root ganglia. Pain fibers (the axons of dorsal root cells) enter the spinal cord through the lateral division of the dorsal root and ascend a short distance (about two segments) in the dorsolateral tract of Lissauer to synapse in the substantia gelatinosa Rolandi. The neurons of the second order cross almost immediately through the ventral commissure to the opposite side and gather as a more or less compact, discrete bundle of ascending fibers (the lateral spinothalamic

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tract) in the anterior half of the lateral funiculus. As the lateral spinothalamic tract ascends, fibers from each higher segment are added to its ventromedial border so that in the cervical region the most posterior and lateral fibers are from the sacral segments with lumbar, thoracic, and cervical forming successive anterior layers. This arrangement means that an incision of the tract which misses the more posterior fibers will leave intact some sacral innervation, or if not carried sufficiently anterior, the upper level of denervation will be inadequate.[2] This tract then traverses up the cord to the lateral nucleus of the thalamus and thence to the post central area of the cerebral cortex. The fibers carrying all other modalities of sensation travel up the cord in the ipsilateral posterior columns or in the fasciculus proprius which surrounds the central gray matter. There exists, therefore, a spatial dissociation of fibers carrying pain and temperature sensation from those carrying light touch, position sense, etc.

Following the standard procedure of cordotomy done at the second thoracic level, a sensory level usually is obtained up to the level of the umbilicus (T_{10}). Consequently this procedure is inadequate to accomplish relief of pain in regions cephalad to the lower abdomen. To relieve pain located above this level cordotomy at the first or second cervical level is done. Foerster[1] and later Stookey[7] were among the first surgeons to attempt cordotomy at this high cervical level. It is now recognized that the procedure can be done with a low operative mortality[3,5] and with appropriate relief of pain.

PROCEDURE

The midline skin incision is made over the lower occiput and upper cervical area. The erector spinae and capiti muscles are reflected subperiosteally bilaterally. If a unilateral cordotomy is to be performed, laminectomy of the first and second vertebrae is accomplished and a U shaped dural incision is made so the flap made by the U can be pulled and sutured laterally. This permits adequate visualization of at least one half the diameter of the cord and also permits adequate room laterally for manipulation. The dentate ligament is grasped at the C_2 level, the denticulation to the dura cut and the ligament itself incised as it fans out to make the denticulation just above the C_1 level. The cord is rotated and an incision beginning at the dentate ligament is made approximately 5 millimeters deep. The knife is moved forward to emerge from the cord just anterior to the anterior root (fig. 1). The dura, muscle and skin then are closed successively with interrupted silk sutures.

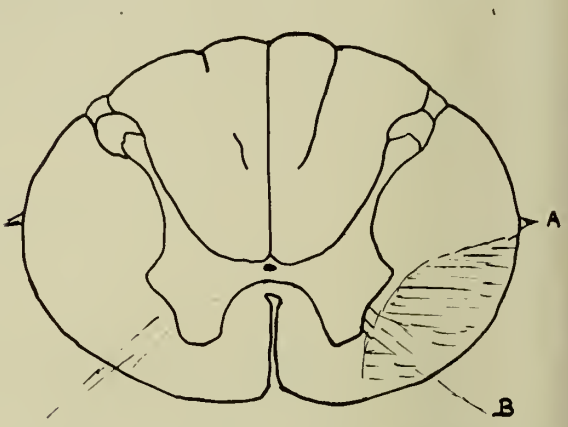

Fig. 1. Cross section of spinal cord at C_2 level. Dentate ligament at A; anterior root at B. Approximate site of cordotomy incision is shaded. Some variation in the extent of the tract has been observed; this is the usual incision made when the patient is under general anesthesia.

If a bilateral cordotomy is to be performed, the only variations from the above technique are to extend the laminectomy to include the third cervical vertebra, the dura opened on this contralateral side, and a comparable incision made at the lower cord level. If the contralateral incision is to be at the second thoracic level, then the laminectomy is of the T_2 and T_3 vertebrae.

The procedure can be carried out either under local procaine or general anesthesia. The patient usually is placed in a sitting position for unilateral cordotomies but if done bilaterally a horizontal position is used. The reason for the latter is that severe hypotension may accompany the second incision. If local anesthesia is used the level of sensory loss can be tested as one extends the incision into the cord. This may help to insure an adequate sensory level without "islands" of retained sensation. However, such "incision-testing" methods are not necessary after the surgeon has accustomed himself to the procedure at this level. If general anesthesia is used it is necessary to carry the incision one to two millimeters anterior to the anterior root to insure an adequate level. Whereas the cord incision at the C_2 segment need be carried only to the anterior root and not beyond it in 80 to 85 per cent of patients,[3] in the others it is necessary to carry the incision to anterior to the root to be certain a high level (C_4) of analgesia is obtained.

The reason for the latter is the individual variation in the location and compactness of the tract.

RESULTS

High cervical cordotomy has been done in this series on 42 patients. In 23 of these it was done unilaterally at the C_2 level. In nine it was done bilaterally in the cervical levels and in ten the high cervical incision was combined with a contralateral incision in the upper thoracic level. The bilateral procedures were done for pain that was located either bilaterally or in the midline such as pancreatic pain or pain arising from metastases to the spine. Chart 1 lists the cause of pain in these patients.

CHART 1.
HIGH CERVICAL CORDOTOMY

Cause of pain	*Number*
Carcinoma, breast	6
Carcinoma, colon	4
Carcinoma, pancreas	4
Carcinoma, prostate	4
Carcinoma, lung	4
Phantom limb pain	3
Tabetic crises	3
Carcinoma, rectum	3
Carcinoma, esophagus	2
Carcinomatosis, primary unknown	2
Arachnoiditis	1
Carcinoma, cervix	1
Carcinoma, ovary	1
Leukemia, lymphatic	1
Chondrosarcoma, pelvis	1
Carcinoma, bladder	1
Carcinoma, kidney	1
Total	42

The pain in all these patients was located in the middle or upper abdomen, in the chest, the arm, or the supraclavicular area. In those instances in which the primary lesion was in the pelvic organs such as the patient with carcinoma of the cervix, the neoplasm had extended out into the pelvis and up into the retroperitoneal space. Pain was present throughout the lumbar region as well as in the pelvis and leg.

Unilateral high cervical cordotomy was done in 23 patients (chart 2). Twenty-two of these obtained complete relief of pain; in one there was no relief. The latter patient had phantom limb pain (fig. 2). Previously a posterior rhizotomy from C_6 to T_1 was performed. This did not afford relief. The cordotomy was done under local anesthesia (fig. 3). Due to a misunderstanding at the time of testing, the highest level of analgesia obtained was at the T_3 level. Usually the level of analgesia is up to the C_4 level. Obviously the inadequate sensory level afforded no relief of pain. This can only be a criticism of the way the procedure was done.

CHART 2.
UNILATERAL HIGH CERVICAL CORDOTOMY

Cause of pain	*Complete relief*	*No relief*	*Deaths*	*Total*
Carcinoma	16	–	–	16
Tabetic pain	2	–	–	2
Phantom limb pain	2	1	–	3
Arachnoiditis	1	–	–	1
Leukemia	1	–	–	1
Total	22	1	–	23

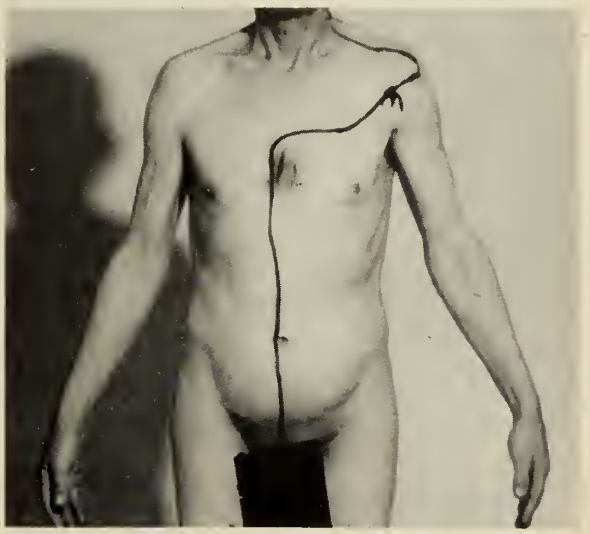

Fig. 2. Photograph of patient with multiple metastases from carcinoma of prostate. Intractable pain was present in left hip and left side of patient's chest. Cordotomy was performed on right at C_2 level. Area of analgesia on left is outlined. The pain was relieved.

Bilateral cordotomy was done in the cervical region in nine patients. The usual site was at the C_1 and C_3 levels although some were done at the C_1 and C_6 levels (fig. 4 and fig. 5). The cause of pain and result in these patients is shown in chart 3.

CHART 3.
BILATERAL CERVICAL CORDOTOMY

Cause of pain	*Complete relief*	*No relief*	*Deaths*	*Total*
Carcinoma, esophagus	1	–	–	1
Carcinoma, breast	2	–	–	2
Carcinoma, metastatic, primary unknown	1	–	–	1
Tabetic crises	1	–	–	1
Carcinoma, pancreas	1	–	1	2
Carcinoma, prostate	–	–	1	1
Carcinoma, rectum	–	–	1	1
Total	6	–	3	9

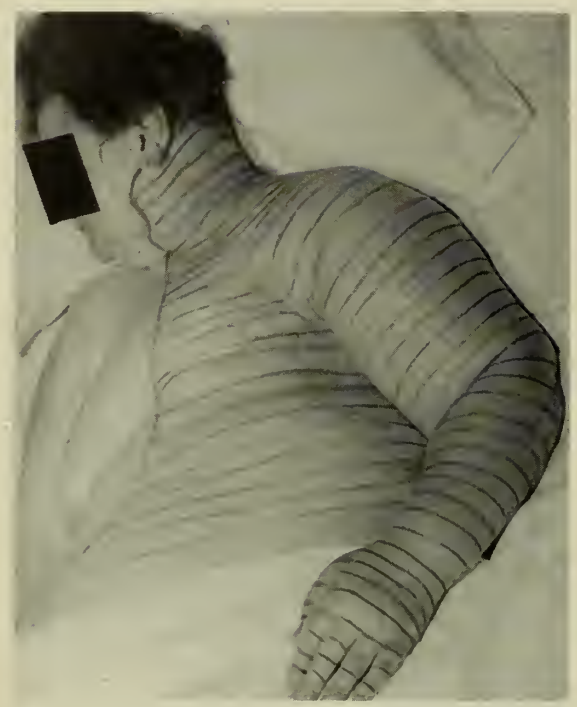

Fig. 3. Photograph of patient who had carcinoma of the left breast. Radical mastectomy was performed. Intractable pain developed in the left shoulder, arm, and chest from extension of the lesion into the brachial plexus. Right sided cordotomy at C_2 level combined with posterior rhizotomy of left C_2, C_3, C_4 nerves. Patient was relieved of pain.

Fig. 4. Photograph of patient who had carcinoma of left breast treated with radical mastectomy and deep roentgen therapy. Intractable pain developed in chest and right shoulder. Cordotomy was performed on right at C_2 level and on left at C_2 level. To raise the sensory level to above the C_4 level on the right a posterior rhizotomy of C_2, C_3, C_4 nerves on the right was performed.

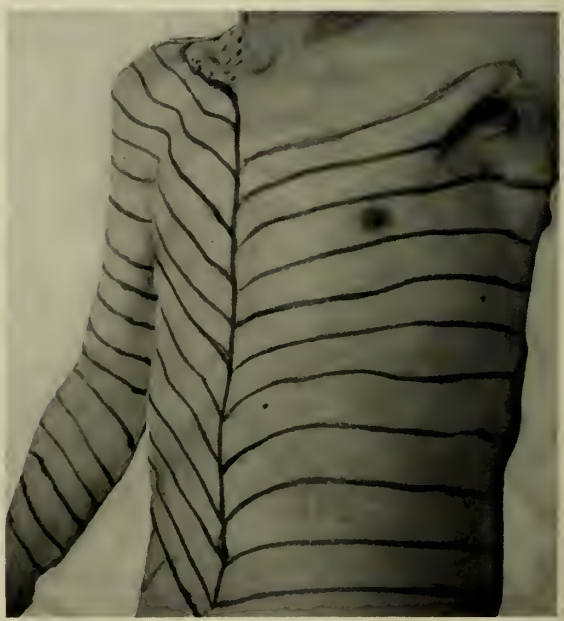

Fig. 5. Photograph of man with carcinoma of pancreas and intractable pain throughout the upper abdomen and lower chest regions. Cordotomy was performed on left at C_2 level and on right at C_4 level. The stippled area on right was made anesthetic by section of the posterior roots of C_2, C_3, C_4 nerves.

The precipitating cause of death in two of these three patients actually occurred without cordotomy incisions being made. One occurred in a patient under pentothal-curare anesthesia, with endotracheal intubation, prior to opening the dura. The patient was in a sitting position. The other patient was under local procaine 1 per cent anesthesia, was horizontal on the operating table, and difficulty occurred just after the dura was opened. Both patients had a sudden cardiac arrest. The chest cavities were opened immediately and cardiac massage instigated. In both patients spontaneous cardiac contractions began but death ensued 48 hours later. The exact cause of the cardiac arrest was not ascertained at autopsy examination. The third patient died three days postoperatively. He had extensive metastases from carcinoma of the prostate. He previously had had a bilateral adrenalectomy. The cordotomy procedure was uncomplicated and postoperatively he had adequate sensory levels to C_4 on one side, C_7 on the other, and was free of pain. Death was due to respiratory failure, cause of which was not found at autopsy examination. Obviously all three patients were poor surgical risks, but it was felt that their pain was so severe that cordotomy for relief was indicated.

High cervical cordotomy to affect the side of maximum or more rostral pain was combined with contralateral high thoracic cordotomy in ten patients. The cause of pain and evaluation of relief obtained is shown in chart 4.

CHART 4.

UNILATERAL HIGH CERVICAL CORDOTOMY COMBINED WITH CONTRALATERAL HIGH THORACIC CORDOTOMY

Cause of pain	*Complete relief*	*Partial relief*	*Deaths*	*Total*
Carcinoma, colon	2	–	–	2
Carcinoma, pancreas	2	–	–	2
Carcinoma, prostate	1	–	1	2
Carcinoma, rectum	1	–	–	1
Carcinomatosis, primary unknown	1	–	–	1
Carcinoma, cervix	1	–	–	1
Carcinoma, bladder	–	1	–	1
Total	8	1	1	10

The relief from pain shown in chart 4 is that from the high cervical cordotomy and not from the side affected by the thoracic cordotomy. Relief obtained with thoracic cordotomy is less complete. In one patient the thoracic incision had to be remade. In two others the relief of pain obtained with the thoracic cut was incomplete but it was adequate to make reoperation unnecessary. The one patient with carcinoma of the bladder who had incomplete relief had an adequate sensory level (to C_4). Why he had recurrence of pain is not known. The retained pain was deep, located in the joints, but due to involvement of the lumbosacral plexus. Perhaps this pain sensation was carried up the posterior columns.[4]

There were two postoperative deaths; one from pneumonia 12 days postoperatively and one from combined operative trauma and debilitation due to cancer.

Complications were observed in these forty-two patients. There were five deaths. Whereas two of these were precipitated prior to making the cordotomy incision and perhaps were not true complications of the procedure, it was felt that they should be included. One of the deaths from atelectasis and pneumonia was undoubtedly precipitated by respiratory distress due to injury to the pyramidal tract fibers resulting in diaphragmatic weakness. Other complications observed included urinary incontinence, motor weakness of an arm or leg or both and postural hypotension. Motor function of the bladder was often impaired but relatively normal function was nearly always recovered in those who did not have contributory factors such as benign prostatic hypertrophy or malignancy involving the bladder or its nerves. The frequency of permanent bladder dysfunction was higher in patients on whom bilateral cordotomy was performed (57 per cent) than in those having unilateral cordotomy (9 per cent). There was undoubtedly a factor of more extensive cancer involvement in the former. Motor paresis of an arm or leg or both occurred in 19 per cent of the patients. In all of these the weakness diminished and was not a serious permanent complication. In bilateral cordotomy, postural hypotension presumably on the basis of interruption of the sympathetic fibers has been a frequent (54 per cent) but temporary problem. All these patients must be told the protective function of pain and temperature sensation has been removed. Occasionally, despite emphatic warnings, patients have injured themselves without realization of injury or else have neglected an injury because it was not painful.

Follow-up to determine the long term results of pain relief in terminal cancer patients has proved a problem. Certainly, some patients may have developed recurrence of pain after they passed from observation. In others, death followed in a few weeks and recurrence of pain might have resulted had there been a longer survival. Cordotomy was not done unless there was a probable survival period of at least three months. In evaluation of the results here reported, relief was considered complete if the operations relieved the postoperative pain since this was the objective of the procedure.

SUMMARY

A series of 42 patients upon whom cordotomies in the high cervical region were performed is reported.

High cervical cordotomy has made it possible to offer relief to a previously unrelieved group of patients. It has been particularly effective in patients with malignant infiltration of the brachial plexus. It appears to be the most effective measure against phantom limb and tabetic pain. It has almost entirely replaced dorsal root rhizotomy except for pain in the upper four cervical segments. Complications appear to be less frequent than with thoracic cordotomy.

There is less variation in the sensory levels obtained with the high cervical operation than with the high thoracic. It is believed the lateral spinothalamic tract is more consistent in its anatomical structure and position at this level.

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The Treatment of Post-Herpetic Neuralgia*

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One of the distressing, baffling problems confronting the physician is the lack of effective therapy for intractable post-herpetic neuralgia. Fortunately in only a small percentage of cases does the pain in acute herpes zoster linger beyond the acute or subacute phase of the disease. However the neuralgic sequelae in those afflicted remains a therapeutic enigma. The beneficial results reported by most authors in the literature apply primarily to the treatment of the pain associated with the acute manifestations of the disease. It is not uncommon for the pain to precede the outbreak of the typical vesicles, to disappear at or during the eruption, or to continue into the post zoster neuralgic state that may persist for years. In a number of cases several weeks may elapse from the termination of the acute stage before the appearance of constant, intractable, or occasionally paroxysmal pains. It is well recognized that post-herpetic neuralgia is prevalent primarily amongst the aged. Hence arteriosclerosis has been cited as a contributing factor. The neuralgic pains are described variously as burning, boring, stinging, crawling, pulling, lancinating, tic-like, etc., which because of their tenaciousness and persistence may lead to abnormal psychologic states including narcotic addiction and suicidal tendencies.

The pathogenesis of post-herpetic neuralgia is not readily understood. Over fifty years ago Head and Campbell[1] on a study of postmortem material in 21 cases of herpes zoster demonstrated lesions in the skin, dorsal ganglia, dorsal roots, spinal cord, and peripheral nerves. An acute inflammatory process is present in the involved dorsal root ganglia and sensory ganglia of the cranial nerves which may extend into the spinal cord and brain. In the acute stage the ganglionitis is marked by mononuclear and occasionally polymorphonuclear infiltration (chiefly perivascularly), hemorrhage, edema, and necrosis. There is a symptomatic variety of herpes zoster which may arise as a complication to some non-specific disease or toxic process. Every case of herpes zoster thus warrants complete study to rule out metastatic carcinoma, leukemia, lymphoblastoma, intoxication with heavy metals, tuberculosis, syphilis, etc.

The mechanism for the production of post-herpetic pain has been attributed by many to the scarring process and persistence of inflammatory changes in the peripheral nerves including the terminal ramifications, the dorsal ganglia, and posterior gray matter. Hyndman,[2] Findley and Patzer[3] suspect that the neuralgic pains are mediated by the afferent sympathetic nervous system and the attendant vasospasm. Browder and de Veer[4] assume that zoster neuralgia results from involvement of the terminal ramifications of the nerve tissue within the inflammatory cutaneous foci in all phases of the disease. However it is then difficult to explain why peripheral nerve surgery, dorsal rhizotomy, and cordotomy have usually proven so ineffective. Dolan and Bucy[5] report the unusual case of a 74 year old adult who developed herpes zoster ophthalmicus a year following retrogasserian neurotomy for tic douloureux. Their patient was without pain throughout the entire course of the disease; however, there is no way of knowing if this patient would have developed post-herpetic neuralgia had he not had the preceding neurotomy. It was therefore concluded by Dolan and Bucy that the peripheral nerve structure serves only as a pathway to the central nervous system and it is not the cause of the pain once post-herpetic neuralgia develops. It is generally known that persistent zoster neuralgia is present chiefly amongst the elderly and it has therefore been suspected that arteriosclerotic vascular changes result in diminished circulation to the involved nervous

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tissue interfering with the metabolism of the previously affected inflamed nervous tissue. Tatlow[6] in reporting his review of 58 patients with herpes zoster ophthalmicus amongst whom only one patient developed severe post zoster neuralgia, requiring alcohol injection, was impressed with the fact that those individuals who continued to have pains following acute herpes were of the introspective, worrying type of personality. Psychologic factors must always be considered in the discussion of pain and its etiology – pain being a common denominator of fear and each new outburst of pain being as severe, if not more so, than the preceding outburst with little or no adjustment of the organism to pain.

Post-herpetic neuralgia is most common in the thoracic area. Zoster neuralgia is next most frequent in the ophthalmic division of the trigeminal nerve. It seldom occurs in the limbs.

MEDICAL THERAPY

Numerous medicaments have been used to control the neuralgic pain. The most commonly used include liniments, oils, iodides, arsenicals, ferrous compounds, narcotics, nicotinic acid, thiamine, posterior pituitary extract, ergotamine, smallpox vaccine, convalescent serum, histamine, and more recently sympathetic blocking agents, antibiotics, Protamide, cortisone, ACTH, and Vitamin B_{12}. Although these drugs have been used chiefly to control the pain in acute herpes zoster with variable success, they have been only slightly effective in the neuralgic cases. Findley and Patzer[3] treated 4 cases of pain during the acute and subacute stage of herpes zoster by paravertebral sympathetic block with good results. Fisher and co-workers[7] used tetraethylammonium chloride in 3 cases of herpes zoster and in 1 case of intercostal neuralgia with complete relief of pain in 2 shortly after initiation of therapy, whereas the two other cases required treatment for one and three months. Combes and Canizares[8] reported the effectiveness of intramuscular Protamide, a denatured protolytic enzyme obtained from mucosal layer of hog stomach, in a series of 50 patients with painful herpes zoster. Excellent results were obtained in 58 per cent, satisfactory in 20 per cent, and unsatisfactory in 22 per cent. The dose varied from 1.3 cc. to 24 cc. They stated that no patient who made an excellent or satisfactory recovery after Protamide therapy suffered from post-herpetic neuralgia. This statement is not startling in that 22 per cent of their patients had poor results and the frequency of post-herpetic neuralgia is seldom higher than 20 per cent. Kass, Aycock, and Finland[9] evaluated the effectiveness of antibiotics in herpes zoster. Twenty-five patients were treated with aureomycin, 25 with chloramphenicol, and 22 with simple analgesics. They noted no measurable superiority of the antibiotics over the simple analgesics. Pain was completely relieved in less than two weeks in over half, irrespective of choice of therapy. Post-herpetic neuralgia occurred in 18 per cent of their cases. Schaffer and Svendsen[10] treated 24 patients with aureomycin and chloramphenicol and a control group of 22 with lactose. They concluded that there was no difference between the treated and control group with regard to duration of skin lesions or neuralgia. Most observers agree that the antibiotics have merit in the treatment of ophthalmic herpes to prevent ocular complications. Weinstein and Lamas[11] reported prompt relief of pain and early regression of eruption in 9 cases of herpes zoster. Cortisone in tablet form, in a dosage of 12.5 mgm. every six to eight hours, resulted in cure in 2 cases of zoster neuralgia and one case of improvement. No neuralgic sequelae in those cases treated early.

Conflicting isolated reports concerning the use of massive doses of Vitamin B_{12}, 1000 micrograms in daily single or divided doses have appeared. The excellent results obtained in the treatment of the paroxysmal pain in trigeminal neuralgia with massive doses of crystalline B_{12} by Fields and Hoff[12] suggested the use of this new therapeutic agent for zoster neuralgia and warrants further investigation. It is suspected that Vitamin B_{12} is important in the metabolism of the sensory neurones.

Filtered irradiation of the involved sensory neurones has proven to be one of the most effective remedies in the treatment of zoster neuralgia, if used before the stage of chronicity and narcotic addiction. Roentgen therapy is usually recommended if the pain lingers beyond that associated with the acute attack. If irradiation therapy is effective, 3 to 6 doses of approximately 80R each on alternated days is sufficient.

Alcohol block of the involved sensory ganglia has usually failed. Alcohol injection of the supraorbital nerve in cases of ophthalmic zoster neuralgia has resulted in occasional success.

As is so true in many diseases with spontaneous relief, it is most difficult to evaluate the efficacy of any therapeutic regime.

The following 3 cases admitted to the Veterans Hospital, Minneapolis, Minnesota, are cited to demonstrate the various agents used:

Case 1: D. A., a 72 year old shipping clerk, was first admitted to the Veterans Administration Hospital 3-27-48, two months after the acute onset of herpes zoster. The herpetic lesions had been present over the left upper chest, scapular area, and posterior aspect of the left arm. Pain of a burning, bruising nature persisted with little relief from local heat and simple analgesics.

The physical examination on admission revealed a blood pressure of 170/110, occasional extrasystoles, scaly erythematous skin lesions from D3 to D6, and voluntary limitation of the left shoulder girdle and arm because of the burning pain on movement. Neurologically, there were decreased abdominal skin reflexes on the right, increased right knee jerk, positive right Babinski, and a hyperalgesic and hyperesthetic area from C7 to D8 on the left. Complete blood studies, urinalysis, and blood serology were negative. X-rays of the cervical and thoracic spine revealed moderate hypertrophic arthritic changes. The spinal fluid examination disclosed 41 mononuclears, 33 mg. per cent protein, a flat gold curve, and a negative Wassermann. The electrocardiogram revealed a left axis deviation with findings of a mild coronary insufficiency. The diagnosis of zoster myeloradiculitis with postherpetic neuralgia was made.

He was first treated with cobra venom 1 cc. intramuscularly with partial relief, but this had to be discontinued because of pain at the site of injection. He then was given a course of a combination of 100 mgm. of Vitamin B_1 and prostigmine 1:2000 intramuscularly for fifteen days with variable mild to moderate temporary improvement. The patient was discharged 5-3-48 and readmitted on 6-8-48 because the neuralgia was unremitting. Paravertebral sympathetic nerve blocks from D2 to D6 using 1 per cent procaine on three occasions resulted in complete relief of pain, lasting however only two hours. He received codeine grains ½ to 1 q.4.h., daily from 6-8-48 to 6-30-48. From 6-24 to 7-24-48, 1000 mgm. of B_1 in 100 cc. of normal saline was administered intravenously with partial relief. He was discharged on pass 7-26 to 8-30 with a neuralgia of less severity. Beginning on 8-31-48 for ten days he received tetraethylammonium chloride (Etamon) beginning with 100 mgm. intramuscularly and gradually increasing to 300 mgm. t.i.d. Six intravenous injections of procaine,. 250 mgm. in 250 cc. of normal saline were also administered as well as ultraviolet and infra-red radiation. On discharge 10-1-48 the patient informed us that he had received the greatest relief from the intravenous massive doses of B_1. He was last seen 6-10-49 when he entered the hospital for a herniorrhaphy at which time he stated his pain was progressively subsiding and it was not necessary for him to take any medications. No further therapy was recommended.

Case 2: F. E., a 54 year old laborer, entered the Veterans Administration Hospital 1-9-50, three weeks after onset of acute herpes zoster in the left fourth thoracic dermatome. The pain was described as a sharp, sticking variety that would last for a few hours or so, relent briefly, and return with equal intensity. As the patient was a moderate alcoholic, self therapy with whiskey had been tried without lasting benefit.

The examination revealed scaling, erythematous lesions of the left mid chest approximately D4 to D5. There was dysesthesia to superficial sensation from D3 to D5. Psychometric evaluation disclosed somatic preoccupation and a definite neurotic profile. The routine laboratory studies including chest x-ray were normal. The spinal fluid revealed 0 cells, 55 mg. per cent sugar, 40 mg. per cent protein, negative serology, and a flat gold curve.

He was first treated with aureomycin grams 1 b.i.d. and subsequently decreased to grams 1 daily for ten days. Because of intense pruritus, local calamine lotion and an antihistamine were prescribed. On 1-23-50 nicotinic acid 100 mgm. q.i.d. was administered and he was discharged with this medication 1-27-50 with moderate improvement. He was next seen on an outpatient visit for continued pain and a left sympathetic nerve block resulted in relief for twenty-four hours. On readmission 8-16-50 a course of tetraethylammonium chloride (Etamon) was begun, starting with 300 mgm. intravenously t.i.d. and gradually increasing to 450 mgm. from 8-22 to 8-30. From 9-7 to 9-20 Priscoline (benzazoline hydrochloride) 25 mgm. q.i.d. was administered and he was discharged with this medication and APC's on 9-20-50 without improvement. When seen a year later (9-24-51) there was continuous pain of a burning and stabbing nature in the region of the left nipple. Protamide, 1.3 cc. intramuscularly, was administered for twenty-three days without relief. On 11-1-51 a left stellate block with 50 cc. of 1 per cent procaine was administered without relief. He received a total of three irradiation treatments totaling 200 R over a period of nine days to the involved ganglia. On discharge 11-27-51 he continued to complain of his pain and he has not been seen since.

Case 3: Rev. B., 60 year old minister, admitted to the Veterans Administration Hospital 8-30-51 and discharged 10-19-51 with a diagnosis of post zoster neuralgia of six years duration. There was continuous aching pain of variable severity, at times excruciating and awakening him from sound sleep. The patient felt quite strongly that his case was mishandled at the onset and that negligence was responsible for his present difficulties. The intractable pain was confined to the left thorax from D3 to D7. In the past he had received various shots, tablets, and several courses of irradiation.

The examination disclosed telangiectasia in the involved skin area. Slight hyperalgesia was present from D2 to D8, most prominent at D6. Routine laboratory studies including spinal fluid analysis were entirely normal.

A ten day course of Protamide, 1.3 cc. intramuscularly, was administered which altered the course and lessened the severity of his pain. A left stellate ganglion block, using 1 cc. procaine and allowing the solution to gravitate down over the upper thoracic sympathetic chain, resulted in partial relief. A repeat block resulted in increasing alleviation with the patient commenting, "I am at least 80 per cent relieved and haven't felt this comfortable for the past six years." No further medication was administered and he was discharged without any. We have no follow-up on this patient.

It is readily seen from the abstracts of these three cases that a variety of remedies were used singularly and in combination. The first patient noted most relief, though temporary, from massive intravenous doses of vitamin B_1, 1000 mgm. in 100 cc. normal saline. Eight months after he

was last treated his pain had gradually remitted, and it is presumed that time alone was a therapeutic factor. In Case 2 aureomycin, sympathetic nerve blocks, Etamon and Protamide in prolonged courses, roentgen therapy, and other supplemental medications proved to be of little or no benefit. Psychogenic factors apparently played a role. Case 3 obtained gratifying relief with several sympathetic nerve blocks, whereas Protamide was less successful. In neither of these cases was surgery contemplated for relief of pain. An opportunity to treat several cases of zoster neuralgia with heavy doses of B_{12} is eagerly anticipated to ascertain whether this new agent will offer as much relief to the patients with zoster neuralgia as it has for those with typical facial neuralgia.

SURGICAL THERAPY

The neurosurgical procedures for relief of intractable pain have also been applied for postherpetic zoster neuralgia and have proven to be equally as disappointing as the medical armamentarium. The nervous pathways have been sectioned at all levels singularly and in combination. The most commonly performed procedures include sympathtectomy, dorsal rhizotomy, anterolateral cordotomy and medullary tractotomy. Other procedures include excision of the involved skin or undercutting denervation, lobotomy and extirpation of the sensory cortex.

Bailey[13] has expressed his opinion that zoster neuralgia was not amenable to surgical relief. In 1946 Bucy[14] polled the American neurosurgeons on their experience in the treatment of post-herpetic trigeminal neuralgia and it was their opinion that trigeminal rhizotomy was ineffective and should not be performed. In 33 instances out of a total of 80 procedures a retrogasserian neurotomy was performed with little or no relief in 29 cases and good results in only 2 cases. Sjöqvist[15] records the failure of trigeminal tractotomy in two cases in summarizing his ten years' experience with this procedure. Caudill, Peyton, and French[16] mention the failure of thoracic cordotomy to relieve the zoster neuralgia and in the same paper record no cure resulting from excision of the hyperalgesic involved skin. Of the five patients they had treated by skin excision, two had much improvement, two some improvement and in one no relief. Browder and de Veer[4] feel that denervating the affected area by excision of the involved skin and subcutaneous tissue merits further use and in their experience this procedure gave a better chance of relief than any other surgical procedure. They performed this operation on four elderly patients with thoracic post zoster neuralgia obtaining excellent results in 2, satisfactory in the 3rd, and a failure in the 4th.

Hyndman[2] relieved zoster neuralgia of the face by ablation of sympathetic cervico-dorsal ganglia whereas trigeminal neurotomy failed. Reichert[17] also mentions beneficial results obtained from excision of the sympathetic chain for trigeminal zoster neuralgia. Dorsal sympathectomy for thoracic neuralgia has not been successful.

Prefrontal lobotomy has been tried in isolated cases. Falconer[18] cites the case of a 70 year old patient who was relieved of his intractable trigeminal zoster neuralgia by prefrontal lobotomy whereas little or no relief resulted from previous surgical attacks including rhizotomy and medullary tractotomy. Sugar and Bucy[14] report the case of a 67 year old male on whom various medicinal and surgical remedies were applied. Bilateral extirpation of the sensory cortex was performed in two stages 10 and 15 months after the acute onset of herpes zoster ophthalmicus. This was also unsuccessful and because of a severe depressive reaction accompanied by suicidal thoughts their patient received electroconvulsive treatments and later a bilateral prefrontal lobotomy with amelioration of his pain and depression until his death 20 months later. Because a lobotomy, fully adequate to relieve one's suffering, usually produces profound personality changes, as loss of initiative and spontaneity, this procedure is reserved for the most desperate cases, and preferably where marked depressive features exist.

Rhizotomy if at all successful must be performed at least on two or three roots above and below the seat of involvement. Likewise a cordotomy must be carried out sufficiently cephalad, several segments above the distribution of the pain, to be certain that the neurones of the second order, that form the lateral spinothalamic tract, have all crossed over. An anterolateral cordotomy is preferred over a multiple rhizotomy, and in virtually all cases of zoster neuralgia of the trunk and limbs to be performed prior to consideration of prefrontal lobotomy.

The various neurosurgical procedures which have proven so successful for treatment of intractable pain of varied etiology have been ineffective in the therapy of zoster neuralgia. Ex-

cision or undercutting denervation of the involved skin promises to be the foremost of the surgical techniques.

SUMMARY

A review of the medicinal and surgical procedures available for the treatment of post-herpetic zoster neuralgia reveals the failure of any particular regime to be uniformly effective.

The experience with 3 cases of thoracic zoster neuralgia and remedies prescribed is presented.

A successful therapeutic is eagerly awaited.

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Current Literature on Pain

CHEST PAIN. Howard Nicholson, M.D., F.R.C.P., *Br. Med. J.*, Feb. 7, 1953, pp. 324-326.

Coronary insufficiency produces retrosternal pain with or without radiation to the arms, jaws, neck or back. Excruciating pain behind the sternum or in the back may result from a dissecting aortic aneurysm. Pressure of an aortic aneurysm upon the sternum, ribs and other structures may cause severe aching in the upper chest.

Peptic ulceration of the distal esophagus is usually associated with gastric hernia sliding into the mediastinum. Hernial symptoms include fullness and discom-

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Book Review on Pain

CAUSALGIA, by Frank M. Mayfield, M.D., assistant professor of clinical surgery at the University of Cincinnati. No. 58 in the American Lecture Series. A monograph in lectures in neurosurgery. Printed 1951. 54 pages, 3 charts, and 12 figures. Charles C Thomas, Publisher, Springfield, Illinois.

The writer feels that causalgia for the time being is regarded as a clinical entity. On the basis of laboratory experiments (1943) the view is advanced that causalgia might result from cross stimulation of sensory fibers due to fiber interaction from the sympathetics within the injured nerve.

The publication is based upon a study of 105 cases of causalgia in military service treated with sympathectomy.

The onset of pain after the injury was instantaneous in about 50 per cent, the remainder from 4 hours to 3 months. The rate of incidence of causalgia after peripheral nerve injury, which is severe enough to give indications for sympathectomy, is about 2 per cent. The symptoms are usually referred to the distal part of the autonomous zone of the injured nerve. The palm of the hand, of the toes, and plantar surface of the foot are the sites of pain. The pain is usually described as burning but also throbbing or aching pain has been indicated by the patients. The pain might be paroxysmal and may change an emotionally stable valiant soldier into an emotional derelict who becomes irritable and shut-in. A psychogenic etiology has been excluded and the psychoneurotic personality is rather a result than a cause to causalgia.

The vasomotor and trophic changes were of two types, the vasoconstriction and vasodilatation. This first group obtained relief from the pain on application of warm packs and the latter group relieved from pain when body temperature was lowered.

Secondary osteoporosis occurred in approximately 20 per cent of patients with causalgia. The danger of drug addiction and compensationitis is great among the patients who are not coming under proper treatment early.

The treatment of choice in causalgia is neurosurgery consisting of interruption of the appropriate sympathetic chain to the painful part. A preganglionic ramisectomy of the second and third dorsal ganglia for the upper extremity and removal of the second and third lumbar ganglia for the lower extremities is performed.

In the final chapter the surgical technique is described, it being illustrated with extremely clear figures, demonstrating the technique.

Procaine block of the appropriate sympathetic chain is a valuable diagnostic procedure. It should be tried prior to surgery. The end results three to five years after surgery show that the patients are relieved of the burning pain. Some are, however, still conscious of tingling and numbness or weakness.

The book is easily read and is strongly recommended for reading to all men in the medical field. E.L.

All inquiries and manuscripts for the Section on Pain should be sent to Dr. John S. Lundy, 102 Second Avenue S.W., Rochester, Minnesota.

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.*

"TRIGGER-POINTS"*

THE terms "trigger-points," "trigger-areas," "trigger-zones" are used with increasing frequency in current medical literature. They are applied most commonly to sites of moderate or marked tenderness in musculo-skeletal structures which, on irritation, produce radiation of pain to other parts of the body. The intent of authors using such expressions is evidently to define the primary source of painful impulses due to injury or disease of skeletal structures from which pain and tenderness are referred elsewhere; in this restricted sense, the terms convey a distinct meaning which is not likely to be misunderstood.

When, however, these designations are used as being synonymous with such lesions as "muscle-nodules," "myalgic spots," "fibrositic nodules," the intended meaning is lost and the reader becomes confused. These "spots" and "nodules," which are evidently secondary, or reference, areas of tenderness, display some of the characteristics of the primary pathologic lesion, such as hyperalgesia on irritation, radiation of pain which is not constant, and elimination of both of these features by local anesthetization. They are often multiple; the tissues in which they develop fail to show any histologic abnormality commensurate with their reactivity to irritation.

The response to irritation of the hyperalgesic zone, manifested by radiation of pain, is purely subjective; it is, furthermore, an inconstant reaction from either primary or secondary lesions.

It would be of value to add, as an additional criterion for use of this term, the demonstration of structural changes or other reliable evidence, to indicate that the site so designated is really the ultimate starting point of the noxious impulses. This should be the most important consideration, even though the radiation of pain on irritation is absent, which is frequently the case.

There is an urgent need for clarification of this expression in order to establish uniformity of meaning.

R. J. DITTRICH, M.D.

*AUTHOR'S NOTE: This term is not commonly found in medical dictionaries. The term "trigger-area" is usually defined as "a sensitive region of the body, irritation of which may give rise to certain peculiar phenomena, either physiological or pathological, in some part of the body.

Current Literature on Pain

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fort after meals, while esophagitis from regurgitation of acidic gastric juice causes intense, burning, retrosternal pain, which may radiate to the back. Pain is not an important symptom of carcinoma of the lower esophagus or gastric cardia.

Tuberculous pleurisy, states Howard Nicholson, M.D., is the commonest cause of pleural pain in adolescents and young adults. The patient shows fever, rapid and shallow breathing, and most important, a friction rub. Patients may complain of lower chest pain for months or years after pleurisy clears and the effusion has disappeared.

Pulmonary tuberculosis: Pain in the chest wall near site of the lung lesion is frequent. Pleural friction rub is unusual, but the association of this type of pain with pleural adhesions seems demonstrated when treatment with artificial pneumothorax is attempted.

Pneumonia: Onset, whether of the acute specific type or an aspiration pneumonia, is frequently associated with severe pleural pain accompanied by a friction rub. Signs of consolidation and the presence of sputum indicate pneumonia, whereas in tuberculous pleurisy effusion develops rapidly.

Chronic bronchitis: Episodes of pleural pain associated with increase in cough and sputum are mostly due to small areas of aspiration pneumonia arising from blocking of small bronchi by sputum and infection of the atelectatic lung beyond the block.

Bronchial carcinoma: When a carcinoma blocks a bronchus, pneumonia or infected atelectasis may develop with pleural inflammation over the involved lung and typical pleural pain. Extension of growth to the chest wall may produce severe pain by involving nerves and ribs.

Pulmonary embolism and infarction: Pain is prominent when infarction follows embolism and is usually present by the second day of illness. The onset of pain is quite abrupt with recurrence of attacks as further emboli reach the lungs.

Bornholm disease: Pain is the most striking feature in this benign condition of probable viral origin, and is commonly felt at the costal margin or upper abdomen, and sometimes in the shoulder. Muscular pain and tenderness elsewhere over the chest is not infrequent. Pain is accentuated by coughing, laughing, yawning, and upon movement. A coarse pleural friction rub is sometimes heard. The disease usually occurs in small epidemics and duration of pain is usually a few days.

Diaphragmatic pain: Patients with intrathoracic conditions associated with pleural pain and in whom the condition affects only the diaphragmatic region, may complain of pain remote from the chest. The most dangerous situation is when the abdominal localization of the pain simulates acute appendicitis or other acute abdominal condition. Respiratory symptoms, such as painful cough or hurried painful breathing, or abnormal signs at the base of the chest, will indicate the source of the pain. Pleural pain from the central part of the

diaphragm may be felt at the shoulder or along the border of the trapezius muscle.

Spontaneous pneumothorax: Onset is sudden in approximately 75 per cent of the diagnosed cases. The patient is seized with pain in the side, usually felt over most of the chest wall, but sometimes severe at the costal margin. In the absence of distinct pain, a feeling of oppression in the chest is common.

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NEUROSURGERY IN PAIN RELIEF. Carrel M. Caudill, M.D., William T. Peyton, M.D. and Lyle A. French, M.D. *Bull. Univ. of Minn. Hosp.* 24:355-366; 1953 (Feb. 13).

When removal of the cause of chronic intractable pain is impossible, surgical interruption of the pain pathways may be necessary.

Bright, pricking pain is carried in thick, rapidly conducting myelinated nerve fibers, while burning skin pain is carried in smaller, more slowly conducting fibers. Aching pains in viscera, muscles and bones are transmitted mainly in sympathetic chains.

Whether or not pain occurs after stimuli are applied to a body structure equipped with pain endings depends upon the integrity of pain pathways, the nature and intensity of the stimulus, and the individual's pain threshold, state Carrel M. Caudill, M.D., William T. Peyton, M.D. and Lyle A. French, M.D., of Minneapolis, Minn.

Referred deep pain is due to spread of excitation in the neuro-axis to other portions of the same segment, or to adjacent segments. Hyperalgesia may follow noxious stimulation of a referred pain area.

Procaine infiltration of hyperalgesic skin and underlying soft tissues reduces pain, but pain is not entirely eliminated until primary afferent impulses either end spontaneously or are surgically or chemically blocked at the source.

Some improvement, but not compelte relief, may follow simple undercutting or excision of an invovled skin segment.

Neurolysis on traumatized peripheral nerves can give partial relief from the pain of a neuroma, but infrequently brings total relief. A new technique leaves the neuroma in situ, but the nerve is twice sectioned and sutured several centimeters proximal to the neuroma. Neurotomy may relieve the pain, but not in all cases.

Posterior spinal rhizotomy can be carried out for relief of pain in the neck, thorax, in an already useless limb, and in primary nerve root involvement. Two or even three roots above and below the primary area must be sectioned for the best results because of invasion of the one dorsal sensory root by fibers from adjacent roots.

Section of the lateral spinothalamic tract in the upper thoracic cord, several vertebral levels above the upper limits of the pain, is very effective. Complete or nearly complete relief of pain in cancer is achieved in the vast majority of patients by a unilateral, or sometimes a bilateral, thoracic cordotomy. Phantom limb pain, tabetic pain, and post-herpetic pain are more difficult to control.

Cervical cordotomy is necessary if pain originates in regions cephalad to the lower abdomen. Complete loss of pain and temperature sensation occurs beginning about four segments below the spinal segment incised. Touch, sensation, position sense and proprioception are intact. Motor function of the bladder may be slightly impaired, and interference with the motor fibers to the diaphragm and intercostal muscles occurs if the procedure is too extensive.

Cervical cordotomy is particularly effective in malignant infiltration of the brachial plexus and is the most effective measure against phantom limb and tabetic pain. If the procedure is done for malignancy, a bilateral operation should probably be done because of the high incidence of postoperative pain on the other side.

Interruption of the lateral spinothalamic tract in the brain stem (medullary and mesencephalic tractotomy) is not too effective at this time.

Lobotomy and topectomy ideally relieve the unpleasantness associated with pain, yet leave the patient intact mentally and completely aware of the pain sensation. Too often, the operation causes profound psychic disturbances, but unilateral lobotomy and topectomy may be effective without such severe mental changes. Prefrontal lobotomy is usually reserved for terminal malignancy with severe pain.

Visceral pain impulses traverse the sympathetic pathways and enter the lateral spinothalamic tract at a higher cord level. The pain of Sudek's atrophy, renal stones, the shoulder-hand syndrome, chronic pancreatitis, cholecystitis, carcinoma limited to viscera, and the pain of causalgia and angina pectoris can be relieved by removal of the proper sympathetic tissue.

The relief of face and neck pain poses special problems. Pain limited to the trigeminal distribution can be relieved by dividing the nerve through a temporal or suboccipital approach. Deep pharyngeal pain is interrupted by intracranial glossopharyngeal section. Pain limited to neck structures is relieved by posterior root section. Frequently, painful lesions involve several nerves and combined procedures are necessary.

Destruction of the spinal cord with alcohol injection can be used in the already bedridden terminal patient.

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VALUE OF REPRODUCTION OF CHEST PAIN. T. J. Reeves, M.D. and T. R. Harrison, M.D. *Arch. Int. Med.* 91:8-25, 1953.

When coronary disease is not responsible for chest pain the patient is more likely to accept the cause as inocuous if the physician is able to reproduce the pain at will.

Careful detailed history must be taken when a patient presents with chest pain. Physical examination of the heart is important. When physical findings are absent, certain procedures not commonly utilized but easily carried out will often yield the correct cause, declare T. J. Reeves, M.D. and T. R. Harrison, M.D.

Attempts to diagnose angina pectoris on the basis of electrocardiograms before and after exercise or ballistocardiograms often are confusing. In most patients with angina the pain can readily be produced by physical exertion. Exercise consisting of climbing stairs at a constant rate is performed before and after sublingual administration of glyceryl trinitrate under conditions individually standardized similar to those prevailing during spontaneous attacks. Exercise should be discontinued as soon as slightest discomfort occurs. The same effort is demonstrated not to cause pain and a significant increase in exercise tolerance is noted after glyceryl trinitrate is taken by persons with angina pectoris.

Pain of skeletal origin is usually determined by carrying out certain simple procedures. Careful pressure on all points of the chest wall should be exerted in both the anteroposterior and right-to-left diameters. Particular attention is paid to the region of the costo-chondral

junctions which are the commonest sites of pain. First percussion of the chest and of the cervical and dorsal spine is employed. Movements of the chest and arms in all directions should be performed with and without resistance. Walking should be repeated with the arms held rigidly at the sides when discomfort develops upon walking. Procaine block of superficial structures may help in differential diagnosis but may occasionally relieve the cardiac pain of myocardial ischemia. Faintness of reflex origin may occur because of skeletal pain.

In most cases hyperventilation due to severe anxiety causes parasthesias in the extremities or faintness. However, chest pain may be produced by the increased muscle tension resulting from carbon dioxide deficiency. The discomfort may be initiated by aerophagia often induced by the augmented respiratory movement. Pain increases anxiety which in turn aggravates hyperventilation. Local conditioning factors as arthritis may tend to sensitize local muscle areas. Satisfactory levels of respiratory alkalosis to reproduce pain caused by hyperventilation are reached most easily by asking the patient to respire at a maximal rate for several minutes while the chest is auscultated. If this test is negative, then deliberate hyperventilation should be performed.

Disorders of the lower esophagus, proximal stomach and gall bladder may give rise to pain resembling that of coronary disease. Apparently these people swallow air and have increased pyloric tone, so the stomach tends to distend with air. Roentgenographic examinations usually do not demonstrate the cause. The patient's individual discomfort can be reproduced by inserting a tube into the stomach and distending the organ with air. Rapid relief is expected when the air is withdrawn. Occasionally the splenic flexure may be the seat of chest pain. History of less discomfort immediately after defecation and more when constipated is often given. Expulsion of flatus may produce dramatic relief. A positive test for the splenic flexure syndrome consists of reproducing the exact pain of the patient by inserting a tube high through the rectum and inflating the splenic flexure.

The pleura, pericardium and mediastinum are common sources of chest pain. Since the relation to respiration is very striking, the effects in various respiratory positions are of aid. The discomfort associated with pulmonary hypertension may mimic that of angina pectoris but is not relieved by glyceryl trinitrate.

All the various procedures which reproduce pain need not be utilized in an individual case. Discrimination is needed in the choice of procedure to be employed. The clue must come from the history, particularly from those aspects dealing with the relationship of pain to body functions tending to aggravate or alleviate it. A systematic method of questioning must be employed. Tests should be considered negative when pain results which bears no relationship to the spontaneous discomfort.

Reproduction of pain is of great therapeutic importance. Anxiety, usually totally unnecessary, is one of the most important symptoms of persons with true or suspected cardiac disease. When the physician demonstrates he can induce the discomfort at will and relieve it at will, the patient tends to experience relief. He is then more ready to accept the physician's explanation that pain is due to a minor disorder.

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THE NATURE AND HANDLING OF PAIN. Leo Rangell, M.D. *Psychosomatic Medicine* 15:22-37, 1953.

Although avoided wherever possible, pain has a protective function. When successfully handled, pain in small amounts is used as a danger signal, or small amounts are tolerated as inevitable. When pain is overwhelming, signs and symptoms of traumatic neurosis result.

The morbid reaction to pain, according to Leo Rangell, M.D., Los Angeles Psychoanalytic Society and Institute, Los Angeles, California, is to seek or to produce, rather than to avoid, the sensation, to feel neurotically satisfying erotism or relief of guilt, or to substitute the pain for something with which the experience is associated in order to get secondary gain as in hysteria or in excessive dependancy.

Neurotic reactions such as fainting, severe anxiety, or panic may be produced in persons of low tolerance by minor amounts, or even the threat, of pain. On the other hand, neurosis may be made unnecessary by somatic pain.

The wide variety of reactions of people in the physicians' and dentists' offices depends largely upon the symbolic meaning of the situation to the individual, especially among patients with a history of punitive parents or traumatizing doctors.

Among the psychodynamic mechanisms which can alone, or in conjunction with other factors, produce hypersensitivity are acute or chronic situational maladjustment, tension and neurotic conflict, anxiety states, phobias, conversion hysteria, obsessive-compulsive states, psychosomatic states and organ neuroses, masochism, drug addiction, hypochondriasis, psychotic states, and mixtures of these mechanisms.

As in organic illness, treatment of psychogenic pain requires that the emotional conflict be localized, identified, diagnosed, and understood. Therapy may be symptomatic or specific.

Symptomatic relief may be produced if the patient is permitted to shift his attention from his emotional conflict by the doctor either diagnosing a plausible but non-existent somatic disease, or giving a "placebo" by which the patient unconsciously agrees to be fooled.

Drug therapy either increases the threshold for perception of pain (aspirin), produces relaxation, apathy, or euphoria (opiates), physiologically opposes the effects of the state of tension (belladonna), reverses the pain-producing psychosomatic conditions (ergotamine tartrate), produces muscular relaxation (tolserol), or artificially removes the emotional tension (sedatives).

Surgery includes rhizotomy, chordotomy, medullary tractotomy, sympathectomy, and frontal lobotomy. Peptic ulcer is approached surgically by abolishing the vagal innervation with the resulting hypersecretion of gastric juice.

Nonspecific psychotherapy may be authoritative, with repression of conflict, or permissive, with freer expression of impulses without guilt, but without insight by the patient into the underlying conflict.

Specific psychotherapy aims at uncovering the emotional conflicts behind the symptom and may be simple or very complicated. Too incisive and vigorous psychotherapy may remove the symptom, but leave the patient without the protection against anxiety the symptom had afforded, so that a severe and widespread psychopathological state emerges.

RELIEF OF PAIN FROM CANCER OF HEAD AND NECK. Thomas E. Douglas, Jr., M.D. *GP* 6;65-70. 1952.

Since pain produces disturbance of function and splinting of the involved area, mastication may become impossible and liquids distasteful for a patient with an oral neoplasm. The resulting hunger and malnutrition further aggravate his weakness and lower the threshold for pain. Nerve blocking by injection offers an effective method for relief of pain in such areas.

Nerve blocking should be done early and should be selective. More nerves are injected as the lesion spreads thus permitting the patient to maintain sensory functions as long as possible without superfluous areas of paresthesia or anesthesia. The patient should receive the nerve blocking injection when the pain is sufficient to prevent complaint about the minimal discomfort of the resultant anesthesia.

Most areas can be injected with 5 per cent phenol solution in 95 per cent alcohol. Phenol is not employed for injection adjacent to a large vessel since sloughing into the vessel and subsequent hemorrhage may occur. Two or three drops of procaine can be added to either solution, but greater concentrations of procaine dilute and lessen the effectiveness of the alcohol. An alcohol injection produces a burning sensation for three to five days. This is prevented by an initial injection of the nerve or ganglion with 1 per cent procaine.

Nerve blocking permits a patient with an intraoral neoplasm to fully open his mouth to admit an x-ray cone. If the x-ray therapy eliminates the growth, the undesiraiblity of the area of anesthesia, lasting for 12 to 18 months, is counterbalanced by the patient's ability to maintain a sufficient caloric intake while the painfully ulcerated, malignant area is healing.

Sphenopalatine ganglion block: Pain of the soft palate, upper tonsillar fossa, and nasopharyngeal areas is alleviated. The earache frequently accompanying a nasopharyngeal neoplasm is usually relieved. One to two cc. of 1 per cent procaine or 95 per cent ethyl alcohol solution can be injected by a route through the posterior palatine foramen and the pterygopalatine canal, or by an intranasal approach.

Inferior alveolar nerve and lingual nerve block: Painful areas of the alveolar ridge, floor of the mouth, side of the tongue, and anterior two-thirds of the tongue and gum may be rendered insensitive by injections of 1 or 2 cc. of procaine or alcohol. Injection is made by either an intraoral or extraoral route.

Glossopharyngeal nerve: Proximity of large vessels and of other nerves makes injection of the main portion of the nerve hazardous. Branches are effectively blocked by multiple, small fractionated injections around the uppermost portions of the neoplasm. Injections consisting of 0.5 cc. of procaine or alcohol are made 1 cc. from the circumference of the lesion.

Other methods: If the patient is in good physical condition and seems to have many months of life ahead, surgical interruption of sensory pathways, those to the head intracranially, and those to the neck paravertebrally, is performed.

When pain becomes severe the action of salicylates can be enhanced by adding codeine. Morphine, Demerol, and Dilaudid may be used in rotation later. Barbiturates are used to provide sleep. Large amounts of opiates and barbiturates are given without hesitation.

X-ray treatment can also be employed for relief of pain. The involved area is made less painful by controlling infection and slowing tumor growth. Sloughing, necrotic areas may be debrided in some cases to lessen infection and odor.

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THE STUDY OF PAIN. Morris Fishbein, M.D. *Postgraduate Medicine* 12:572-573, 1952.

Pain is a sensation which defies accurate measurement. One of the unacheived goals of pharmacologic research is to remedy this situation. While reports are published purporting to measure pain intensity, results are inconstant and unrepeatable.

Present research on pain and its measurement by Henry K. Beecher, M.D. and associates at Harvard Medical School constitute the subject of an editorial by Morris Fishbein, M.D. Among the subjective conditions in relation to pain which this group is studying are the mental state, attention, learning, association, memory, critical judgment and sensory phenomena. Psychiatrists, pharmacologists, physicians and drug manufacturers find a mutuality of interest in these conditions. The drugs chiefly concerned are the central nervous system depressants, and man is perforce the laboratory animal. Currently analgesic agents are commonly screened in lower animals. The tests depend on abolition of various reflexes. Notwithstanding, the relationship between pain-relieving potential and depression of reflexes is still vague.

The Harvard group is convinced that the use of pain of experimental origin in man is artificial. Natural pain must be the variable on which valid conclusions are based. They form this concept from the observation that emotion can block pain. Extrinsic factors and lack of attention to wounds as in games or during fighting can block pain. In short, a great difference exists between experimentally induced pain and the pain of the patient in the sickbed.

A technic was developed by the Beecher group which can differentiate satisfactorily between aspirin and a placebo, or aspirin and morphine. One experiment had as its object comparisons of capsules containing placebos and capsules containing analgesics of the narcotic class (e.g. morphine). All capsules were identical in appearance. A technic of thorough randomization was found to be essential with the order of agents used varying from time to time. Some individuals were found who are termed "placebo reactors" because they respond favorably to placebos far beyond the responses of other individuals. These people are not malingerers or neurotics but allowance is made for a certain percentage of such persons in every group of people tested.

This experimental team is making a distinct contribution. Their newer methods are far superior to the old-fashioned method of simply distributing drugs to practically everybody and then by trial and error arriving at an exact evaluation. This quotation by Dr. Beecher points up in part the motivation for the new trend in this research: "After all the centuries morphine or opium has been used, common sense in this country has arrived at a dose that is twice as large (15 mg.) as the one that gives essentially the maximum pain relief (8 mg.)".

The Worth of A Modern Hospital to A Community

This is an important Calendar Day in the history of Hudson and its environs on both sides of the St. Croix River. Today, we celebrate the opening of an ultramodern Community Hospital, which from the architectural and planning points of view is everything that skill and thoughtful care can provide. It is a day of Thanksgiving — a time when many a silent prayer of gratitude will be offered up to those forward looking citizens of this area who were responsible for the birth of the venture and who gave liberally of their time and of themselves to bring this significant community enterprise to fruition.

How proper that the ceremonies of dedication are performed in this High School! We are all engaged in the learning process in the "School of Experience," whose tuition fees are the highest of all schools in the world. It is good for all of us to be back for a day at school again, from which vantage point all of us launched our careers.

Perhaps no institution has come up so much in public esteem as have our hospitals during the past century. This circumstance is owing directly to the improvement of the character of the work done in them. One hundred years ago, hospitals were few. Only medical problems of the gravest concern were dealt with in hospitals. The public had great dread of them and rightfully so. In the minds of many up until 75 years ago, hospitals were looked upon as Houses of Pestilence, where erysipelas and infectious fevers, then frequently called zymotic diseases, prevailed. In the intervening years, these diseases have disappeared. In fact, the term zymotic has disappeared from the present-day medical dictionary. All traces of the earlier fear and suspicion of hospitals have also disappeared.

How has this come about? Through improvements in the art and practice of medicine which in turn are direct fruits of research. Today, the Hospital has come to rank with the Church and the School as indispensable Public Institutions. Today people when ill go freely into hospitals for diagnostic and therapeutic procedures, recognizing that they can be cared for there with convenience, dispatch and the greatest safety to themselves.

FUNCTIONALIZING AN ARCHITECTURAL TRIUMPH

A Hospital, like a house, is the work of architects and planners. It takes the devoted love of individuals to make a home out of a house. Be a house ever so elegant, the individuals who reside in it can bring it next door to heaven or hell. What power and majesty there is in every individual if he will only incline his sympathy to the welfare and the good of his fellowman, a pursuit which brings comfort and peace to the human spirit. Unselfish service to our fellowman remains as always the highest of all callings. If every man and woman whose activities center about this hospital will take and observe a pledge to dedicate their lives to the welfare of the patients who come here seeking relief from their distress, this hospital will become a haven for the sick and fulfill the hopes of its founders. It is up to the individuals who will man this hospital, to make it functional. Unless the work of the physicians, the nurses, the kitchen laundry, office and ward workers is well done, the hospital will remain only an imposing edifice.

THE MEANING OF THIS HOSPITAL TO THE COMMUNITY

Ever since Adam and Eve were driven out of the garden of Eden, man has been in need of sympathy for the many difficulties which hedge about the problems of living. Life to many is a series of crises. Samaritanism, or a real concern for our brother's needs, has come to be regarded as that quality of man which most closely approaches the divine. Illness comes eventually into ever man's life. This community, without a hospital for a long time, will find how much such an institution can contribute to the life of this area. In any conflict in life, what combination of forces can overcome the combined strength of *Need* when accompanied by a great *Cause?*

This hospital will serve this community in many ways. It will give employment to many. It will mean increased local expenditure of funds, which in the ultimate will redound in part to the hospital, to help energize its program. It will enrich the lives of the physicians of this area by according them a suitable place to do their work, thereby affording them a source of great satisfaction. What emolument is more acceptable than satisfying labor?

The Hudson Memorial Hospital will come to have a special meaning to everyone whose life it touches. To some it will mean a job, a source of sustenance. And while in the lives of some, that useful purpose will be served by it, let us hope that the lives of all who come directly in contact with its work will be touched in a more significant manner. To some, this hospital will become a symbol of restoration of life and usefulness—a creator of happiness. In the trials of physical illness many a man learns that his most important possession is health and life—far more important than money and material possessions. Then it is a man is inclined to agree with that ancient philosopher who remarked that, "Money is like manure — best when it is spread."

Many will come to look to the Hudson Memorial Hospital as an Angel of Mercy and a safe refuge in time of trouble. And to all, whose lives it touches, let us hope that this magnificent structure will become synony-

*Presented at the dedication exercises of the Hudson Memorial Hospital, Hudson, Wisconsin, in the Hudson High School, January 18, 1953.

mons with kindliness, patience, sympathy, understanding, and wisdom. And let all who do the work of this hospital remember always the great power of gentleness. While the contemplation of what this hospital will mean to this community will engender sentiments of hope and faith in the minds and hearts of all who come here for the relief from illness, pain and suffering, let us jointly plead that an aura of Christian charity always will hover closely around the elements of persuasion which here will become deciding factors involving matters of life and usefulness: "Though I speak with the tongues of men and of angels and have not charity, I am become but sounding brass and a tinkling cymbal."

On the occasion of the publication of his famous dictionary in 1755, Samuel Johnson addressed a letter to the Earl of Chesterfield which in itself was a document of great importance in freeing literature from the burden of patronage. Said Johnson: "Is not a Patron, my Lord, one who looks with unconcern on a man struggling in the water and when he has reached ground encumbers him with help?" Will Mayo was fond of drawing a distinction between internists and surgeons on this basis, adding good humoredly that a surgeon was one who yanked off his coat and dove into the water to pull a drowning man out, without awaiting the outcome of the struggle before offering his help. If any one of you have sat on the Wayside of Life as spectators of this important community venture, it is still not too late to become a patron of the Hudson Memorial Hospital, for the needs of a hospital are continuing and endless.

All who serve this hospital with a spirit of devotion in any of its many important functions becomes a patron of this hospital. When Walter Cannon, world-famous physiologist who grew up in this community was 10 years of age, his dying mother called him to her bedside and said: "Walter, be good to the world!" What sound advice! And that the submissive Walter headed his mother's sage counsel, we all know to our good fortune.

If today, we utter a prayerful hope for the future of this institution and the men and women privileged to serve it, let it be: Bear in mind the welfare of the Hudson Memorial Hospital and its altruistic purposes. What is the good of prayer It does not change the laws of nature. But self-communing often enlarges and quickens the spirit of a man and strengthens his determination. Even the Master at Gethsemane availed himself of the assurance and comfort of prayer. And having composed himself, the Great Master went with quiet resolution and a tranquil spirit to his trial and crucifixion. What an important lesson for all of us!

A year ago, one Sunday morning in Dallas, Texas, the following story was told over the radio by a minister: He said he had called on a sick parishioner in the environs of that city. When the preacher came out, a small son of the sick father whom the minister had visited, was admiring the minister's shining new Cadillac automobile. The minister explained: My brother who has been very successful gave me this wonderful car. Said the little boy: "When I grow up, Parson, I would like to be a brother like that." The Hudson Memorial Hospital, and the world needs persons who would like to be such a brother.

THE GROWING COMPLEXITY OF MEDICINE

Medicine can not be practiced today with a prescription book, a doctor's handbag, and kind words alone. It is far more complicated today. Diagnostic tests and therapeutic devices, of many varieties unknown a generation ago, have made this a far safer world in which to live when illness threatens than our parents found it to be. Moreover, through the agency of research, new techniques and approaches to problems are constantly being learned.

It is fitting that those responsible for the policies of the Hudson Memorial Hospital have appointed to the staff competent specialty consultants who will help resolve some of the difficult diagnostic and therapeutic problems that will arise here. A general practitioner is the backbone of medical practice in America. He has to be able to give useful advice and help in any type of medical problem. That is a large order! He must, in fact, be an extemporaneous artist with some suggestion of solid competence. It is obvious, therefore, that he will need, in many areas of his work, the help and guidance of those with greater experience in more limited areas of interest. The public has the right to expect that the problem of partition of responsibility in difficult cases and situations will be resolved always in the best interests of the patient. It is a problem of great concern to the public. The Hudson Memorial Hospital stands as a symbol of the virtue of community planning. Perhaps here too, it can show the way in another problem important to both the public and the profession.

The lament of everyone — patients and physicians alike — is that all of these things are so complicated. What many would like of course would be the universal specific which taken with a swallow of water after breakfast would protect us from all illness. And failing that, to have a specific antidote for any given illness, taken any time, even up toward the last breath, which would neutralize at once all the enervating and devastating effects of that illness. Yes, it would be wonderful if it were that simple. There are still Ponce de Leons looking for the fountain of eternal youth, and if all youth only had the wisdom to know that those are the glorious years of life, when the foundations of the future are being built! But the making of an excellent dinner, the construction of an automobile, the building of a hospital — none of these are accomplished by merely wishing the task done.

The transition from chaos to clarity, from ignorance to enlightenment, from a plan to its accomplishment — none of these are made in one leap, but by a succession of small, yet often intricate steps, involving the help of many hands and minds. Progress in any endeavor is always like that. As one looks back from the vantage point of fulfillment and achievement with post-mortem wisdom, the path often seems shorter because the steps of entanglement and the advices of confusion are now recognizable.

When Hudson's first hospital, the Oliver Wendell Holmes, was opened in 1887, 66 years ago, there were relatively few specialists in the field of medicine. Many specialties unknown and unnamed then have since come into being. Neurosurgery, pediatrics, psychiatry, and roentgenology are all new and important areas of specialty practice. In addition, there are also a large number of new research techniques which have come to be important enough to warrant the establishment of departments in medical schools to give impetus to development in these areas. Holmes wrote a dedicatory poem for the occasion. If Holmes were alive today to write another poem of dedication for this hospital 66 years later, a spirit of greater buoyancy would be more in evidence than in Holmes' poem of 1887. Accomplishment renews the springs of hope. If Holmes' poem, in certain respects, suggests an effort directed at lifting a veil of gloom from the atmosphere of hospitals of that

day, it should be remembered, that the shackles of infection and suppuration which had manacled hospitals to the tradition of fear and suspicion had yet not been completely severed.

While we all rebel against the mounting costs of adequate medical care in the management of illness, there will be those who will want to express a silent prayer of thanksgiving for the circumstance that, what would have been a miracle a few years ago, has now become in many areas of work an everyday possibility through the agency of research.

The increased cost of living has touched in some manner the lives of all families in the world. The combativeness of the human spirit, his inability to get on with himself and his fellowmen — the struggle for advantage and supremacy — a continuous arming for war — these too pyramid the cost of living, and the cost of medical care as well.

Public philanthropy to medicine crept into evidence approximately 75 years ago. It was then and now continues to be a measure of the increasing confidence of the public in the broad aspects of medicine. The *Hospital* has come to rank with the *Church* and *School* as representing indispensable public institutions in which unselfish and devoted service, at the highest possible level is given freely to the individual and the community. May this and all hospitals always continue in the public favor and have a good name! As you, the citizens of this area, recount with a sense of real satisfaction and accomplishment your good great fortune in having here at your very door such a wonderful hospital, let me remind you too of the great obligation of society and all hospitals to the research done in our universities, without which the miracles of today could not be enacted daily in hospitals throughout our land.

On an occasion such as this, it is fitting that we extoll the potential important contributions of such institutions as the Church, School and Hospital to our communities and to our lives. There is no suggestion of apathy here on the part of the community in this venture. May it always be so. And if Church, School and Hospital in this community can cooperate effectively for the public and individual good, the community of Hudson may well teach all of us an important lesson in getting on with our fellowman. The noticeable spirit of voluntary participation in this effort is very reassuring. It probably remains an untapped source of great community strength, everywhere throughout our great land.

MAKING DREAMS COME TRUE

To have the ability to do the day's work day by day is in itself a significant component of greatness and an important element in the success of any endeavor. There is a certain insincerity in the man who tells you of his dreams, but who makes no sustained effort to translate them into reality. "Behold, this dreamer cometh" has long been symbolic of the world's impatience with dreamers. Yet, Joseph had the ability to translate dreams into action. His dreams made it possible to store food in time of plenty and to feed a populous country and the less provident tribes and peoples of adjacent countries during the time of famine. I believe it would be proper to call Joseph the world's first banker.

There are traces amongst some medical specialists, who affect a particular concern for man's behavior, of attributing more importance to the dreams of sleep than those of the waking hours. Some of you may recall the humor of this situation as portrayed a few years ago in the *New Yorker*. Two middle-aged women, crossing a pasture, took refuge from a pursuing bull in a tree. Said one to the other: "If this were a dream, it might have real significance!" Tell me what a man dreams of and yearns for when all his senses are alive and I will tell you what manner of man he is.

In this world everything is transitory. Nothing lasts. Look about you, the houses, barns, fences and roads that were built 75 years ago, though they stand, they have been refurbished many times by the care and thought of many hands meanwhile. And so it is with everything. All any one of us eventually retains is what he imparts or gives to others: affection, care, devotion, and instruction. The greatest lesson of the Bible is that to find oneself in life, he should give his life to a good cause, holding nothing back. A dedicated life is a useful and a happy life.

Late one August afternoon last summer, my son and I were awaiting the arrival of a taxicab to take us to the railway station. As the taxi arrived, a delivery truck drove up with a box of large, luscious Colorado peaches, which had come as a gift from a grateful patient. We were closing the house for a week and we debated for a moment what to do with them. We quickly put the top row into paper sacks and gave them to our neighbors. The remainder we put in a cool room in the basement. When we returned after a week's outing, not one edible peach remained. We saved only that portion we had given away. This story can be duplicated many times in every man's life. Only the portion we give away is that which we keep in the affection and gratitude of other men. All else perishes. Devoted, loyal service to a good cause is never lost. A generous spirit helps to make dreams come true.

A certain mature realism also is necessary. A man begins to show signs of maturity when he recognizes there are certain things he can not do. It is equally important to know what one can not do, as to know what one can do. Some men pine their lives away dreaming of exerting a great influence in their community; of rebuilding the social structure of the world; of leaving an important legacy to humanity and posterity. The first evangelism of such a dreamer should be with the dreamer himself. A large number of qualities of heart, mind and hand are necessary to convert a dream into reality: amongst others, imagination, generosity, maturity, and a capacity for planning, method, inventiveness, study, persistence, daily satisfaction with small gains, and a practical hard-headed sense of reality. It is not an easy nor a task quickly accomplished in any important endeavor.

The Hudson Memorial Hospital obviously is a cooperative community venture in the true sense of the word. Let us hope that the level of interest in this hospital by the entire community always will continue high. And as we dedicate the Hudson Memorial Hospital today to the service of our fellowmen, let us remind ourselves that the aspirations and dreams of the founders of the Hudson Memorial Hospital and the fortunes of the institution are in the hands of those whose responsibility it is to functionalize this hospital. If they dedicate themselves to their tasks with devoted, loyal and unselfish service, this hospital will become a haven and a refuge for the sick. It can become an institution which will illuminate and brighten the lives of all who enter its portals. The Hudson Memorial Hospital is truly an important community asset. No community should give its laurel wreath to mediocrity. If those, whose responsibility it now becomes to functionalize this hospital, can match the skill and the accomplish-

(Continued on page 304)

Neurosurgery in General Practice, by Adrien Ver Brugghen, M.D., Ch.M., M.S., F.A.C.S., medical professor of neurosurgery (Rush), University of Illinois College of Medicine, neurosurgeon to the Presbyterian Hospital of Chicago. Springfield, Illinois: Charles C Thomas. 665 pages, 282 illustrations. $15.00.

The rapid development of neurosurgery in the last few years, and the wide availability of neurosurgeons today, suggests that the medical profession should have a broad understanding of the problems in this field. This book was designed to help the general practitioner with his neurosurgical problems, particular stress being given to the care of emergency conditions, and to the diagnosis of less acute conditions of the nervous system where there is a possibility of successful neurosurgical intervention. The subject matter is complete and it is interesting to note the number of pages devoted to various topics, e.g., trauma to the central nervous system covers 136 pages, while cerebral tumors have only 12 pages. This would seem to be more in alignment with the general practitioners' interest than in the usual text. Further, the more benign tumor syndromes received more attention. Spinal cord tumors and cerebellar tumors in children received 30 and 36 pages respectively. Herniated nucleus polyposis, trigeminal neuralgia and cerebral vascular accidents are afforded longer discussions, while the less frequent conditions received shorter but adequate treatment.

The author has succeeded in avoiding long descriptions of operative procedures and other esoteric subjects which would be of interest to the neurosurgeons alone. The emphasis is on the diagnosis and the treatment which lie within the realm of the general practitioner, although the various procedures employed by the neurosurgeons are clearly outlined.

Prognosis of the various conditions is indicated and in general the treatment and opinions outlined in the text is the standard of most neurosurgical clinics. The book is well written and well printed and lends itself for cover to cover reading. There are many good illustrations and case summaries throughout the book, as well as short summaries at the end of each chapter which should aid in quick reference work. The bibliography at the end of each chapter is short and refers to English articles in the more available journals.

This book should be of interest to all physicians, but is recommended most highly to the general practitioner. P.S.B.

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Ruptures of the Rotator Cuff, by H. F. Mosely, M.A., D.M., M.Ch., F.R.C.S., F.A.C.S., Hunterian Professor, Royal College of Surgeons of England, Assistant Professor of Surgery, McGill University, Associate Surgeon, Royal Victoria Hospital, Montreal, Quebec, Canada, Charles C Thomas, Springfield, Illinois, 1952.

One of the most perplexing problems that confront the average practicing physician is a complaint of pain in the shoulder region. The many conditions that are manifest with this symptom, are at times extremely difficult to evaluate. Frequently a definite diagnosis can not be established. A publication dealing with one phase of the problem should be generally accepted as an aid in determining some of the occult features. This monograph presents the aspect of rotator cuff injuries.

The contents are derived from an end result study of 31 cases, all of which were extensive tears proven by surgical exploration. Of these cases, 20 were acute and 11 chronic ruptures of the cuff structure. The opinion advanced emphasizes the treatment of choice as early operative repair. It is here that the discriminating reader will find reason to question the conclusions. It becomes apparent immediately that a large number of patients must have had this type of injury previously and obtained satisfactory results with conservative care. Yet this point is not discussed.

The structure of the book, radiographic reprints and illustrations are excellent. The bibliography will afford adequate source material for more interested students. Particularly commendable is the clear and concise printing that features the volume and affords leisurely reading. The intent of the book is to stimulate interest in rotator cuff injuries as a basic cause of shoulder pain. This is accomplished. It is unfortunate that a comparable series of nonoperative cases is not used for analogy.

As a record of a rather prolonged study on the problem, it is a significant contribution. One must be cognizant that this operative approach reflects this opinion of an author with a limited series. That this method has some merit is beyond question; that it is not the final answer is self-evident.

• E.H.O'P.

B-Vitamins for Blood Formation, Thomas H. Jukes, Ph.D., Lederle Laboratories Publication No. 146, American Lecture Series. Charles C Thomas, Publisher, Springfield, Illinois, 1952. 110 pages.

This little monograph is written and printed in readable fashion and is an excellent review of the relationships of the B-complex vitamins and blood formation. Pteroylglutamic acid and vitamin B_{12} in the treatment of the megaloblastic anemias, the chemistry of these substances, and their distribution in natural substances are discussed in some detail. A brief chapter is devoted to the intrinsic factor and its relationship to vitamin B_{12}. A summary of studies on antagonists of pteroylglutamic acid and, in particular, the effects of "Aminopterin" presents a clear review of this subject. The citrovorum factor was separated from vitamin B_{12} in 1949 and the literature on this subject is reviewed in some detail. References at the end of each chapter will be of great aid to anyone interested in the B-vitamins and their effects on blood formation. R.L.T.

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Acute Peripheral Arterial Occlusion, by William D. Holden, M.D., 1952. Springfield, Illinois: Charles C Thomas, 55 pages, $2.35.

This discussion of acute peripheral arterial occlusion is timely and should be well received by surgeon and internist alike because of the inadequacy of authoritative knowledge in this field and because the author speaks authoritatively in this field. A better understanding of the development of collateral circulation and the relation of the autonomic nervous system to vasomotor tonus as well as the investigation and clinical use of anticoagulants have been important factors in more effective diagnosis and treatment. C.A.McK.

American College Health Association News . . .

Doctors Ruth Boynton, Herbert R. Glenn, Joseph Garnet, and Paul L. White constitute a special committee on safety. The National Safety Council is cooperating with the committee in a pilot study in approximately a dozen institutions to secure a picture of the accident problem among college students for which treatment is provided at the health center. Dr. Vivian Weedon and Mr. Gene Miller of the National Safety Council will prepare the accident reporting forms and will analyze and tabulate the data.

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The Council voted to actively support the National Conference for Cooperation in Health Education by participation in its program and payment of annual dues. The purpose of the National Conference is to coordinate the resources, facilities, and activities of the sixty-two official and voluntary education and health member agencies for the purpose of improving school and community health programs for children and youth.

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The request of the Virginia colleges and universities to form a section of their own was approved by Council action.

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The resolution presented by the Illinois Section with the recommendation that it be sent to the Department of Immigration was adopted by the Council. The resolution is as follows:

"The American College Health Association wholeheartedly supports the Department of Immigration in its attempt to find ways and means of securing better screening of foreign students and faculty in regard to health, particularly tuberculosis and emotional problems."

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The annual meeting of the South Central Section was held April 25 at the University of Kansas. This section has a membership of forty-one colleges and universities. The new slate of officers includes:

President—Dr. Ralph I. Canuteson, University of Kansas, Lawrence; vice-president—Dr. George X. Trimble, University of Missouri, Columbia; secretary-treasurer—Mrs. Alta Bergquist, R.N., Nebraska State Teachers College, Kearney; members-at-large—Mrs. Ruth Matthews, Nebraska State Teachers College, Peru, Carin Degermark, Cottey College, Nevada, Missouri.

The University of Missouri campus at Columbia will host the section in 1954.

The program was enthusiastically received and stimulated a great deal of discussion. The one day meeting featured three panel discussions as follows:

Administration Views of the College Health Program: Harold S. Diehl, M.D., Dean, School of Medicine, University of Minnesota; R. G. Gustavson, Ph.D., Chancellor, University of Nebraska; Thomas A. Spragens, A.B., President, Stephens College; Rees H. Hughes, M.A., President, Kansas State Teachers College, Pittsburg; Franklin D. Murphy, M.D., Chancellor, University of Kansas.

The Objectives of a Mental Health Program in a College: Sigmund Gundle, M.D., Health Service, University of Kansas; James N. Haddock, M.D., Health Service, Washington University; Kenneth Anderson, Ph.D., Dean, School of Education, University of Kansas; William G. Craig, M.A., Dean of Students, Kansas State College; Mrs. Frances S. Nelson, Lawrence, Kansas.

Health Service Problems in the Smaller Colleges: C. C. McDonald, Ph.D., Wichita University; Mrs. Alta Bergquist, R.N., Nebraska State Teachers College, Kearney; Mrs. Ruth Matthews, R.N., Nebraska State Teachers College, Peru; Frank A. Trump, M.D., Ottawa University, Ottawa; Miss Carin Degermark, Cottey College, Nevada; E. E. Feind, M.D., Missouri School of Mines, Rolla.

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The papers in our Proceedings are analyzed and indexed in the Education Index by The H. W. Wilson Company, publishers of indexes and reference works.

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April was a busy month at the Infirmary of the University of Florida Health Service, reports Sanford E. Ayers, M.D., the director. The types of disease incidence, however, was normal for this period of the year. Sixty-four cases of rubella raised fears of an epidemic of this disease, but fortunately the number of cases decreased.

The student health staff for the second year performed the physical examinations required for candidates for the Advanced Army R.O.T.C. Dr. Henry W. Deurloo was given direction of this work. All the doctors, several nurses, and the laboratory technicians, participated in the examinations. Dr. Deurloo saw the majority of those who had to return for rechecks, and he also had the task of completing and checking all the forms. Any one who has had experience with these rather complicated Army forms will realize that completion of this work was no small task. There were 321 students examined, 240 visits were necessary for rechecks, making a total of 561 visits for the completion of the requirements. The laboratory cooperated by doing 342 tests for the candidates.

* * *

A two-day conference for School Food Handling Personnel was held at Xavier University of Louisiana on Wednesday and Thursday, April 29th and 30th, in the Xavier University cafeteria, according to Warren McKenna, director of the school's student health service. Special guest of the meetings was Mrs. Thelma C. Morris, health educator of the National Tuberculosis Association. Twenty food handlers from various schools in this area received certificates of merit at the conclusion of the meetings. An exhibit arranged by Blanche Curry, of the New Orleans Tuberculosis Association, was well received by the delegates.

Official greetings were extended by Sister M. Helene, S.B.S., dean of Xavier University. A lecture on personal hygiene was presented by Miss Curry, and Asa Atkins, a member of the Xavier faculty, spoke on food storage, preparation and refrigeration. The program closed with a showing of the film "40 Billion Enemies." The Thursday night session included a lecture and demonstration on food display and service by Hiram Workman of the Xavier faculty and also a talk by John Harris of the New Orleans Tuberculosis Association.

* * *

A part time psychiatrist has been added to the health service staff at Occidental College, Los Angeles, California. Dr. Dale W. Hurley, a graduate of the University of Nebraska and a diplomate of the American Board of Psychiatry and Neurology, has been in private practice in Pasadena, California. Occidental has an enrollment of approximately 1,300 students.

News Briefs . . .

North Dakota

MINOT became the "Mecca" for North Dakota medical men when the 66th annual meeting of the state association and the seventh annual meeting of the Women's Auxiliary convened there. Newly installed president of the association was Dr. Joseph Sorkness of Jamestown; appointed president-elect was Dr. P. H. Woutat of Grand Forks. Other new officers included Dr. D. J. Halliday of Kenmare, first vice president; Dr. R. H. Waldschmidt, Bismarck, second vice president; Dr. G. A. Dodge, speaker of the house; Dr. R. E. Leigh, Grand Forks, vice speaker; Dr. E. H. Boerth, Bismarck, secretary; and Dr. E. J. Larson, Jamestown, treasurer.

Three new district councillors included Dr. O. A. Sedlak, Fargo, first district; Dr. Nelson Youngs, Grand Forks, third; and Dr. R. B. Radl, Bismarck, sixth.

The association went on record approving measures to improve press and radio relations with the state society.

On the women's side of the meeting, newly installed as president of the Auxiliary was Mrs. L. Henry Kermott, Minot, and as president elect, Mrs. S. C. Bachellor of Enderlin. Other officers included Mrs. J. H. Mahoney, Devils Lake, first vice president; Mrs. Charles A. Arneson, Bismarck, second vice president; Mrs. John Jansonius, Jamestown, recording secretary; and Mrs. V. J. Fischer, Minot, treasurer.

° ° °

THE NORTHWEST CLINIC in Minot celebrated its 25th anniversary recently with an "open house" for the public, according to Dr. Angus L. Cameron, director of the clinic. About 500 people "went through" the clinic that afternoon — a visit on a purely social basis including refreshments in the cafeteria. The original clinic was a three-story building erected in 1928 — the first instance of group practice in the medical specialties in that community. Then in 1949 a new six-story addition was planned and constructed, with the first building left intact as an integral part of the clinic. The Northwest Clinic employs more than 55 persons, and handles 150 to 200 patients each day.

There is an invisible part of the clinic which nevertheless is very concrete, and that is the Medical Foundation plan which was designed primarily to aid residents and internes, and now is being used to help send selected graduates of the University of North Dakota away for their clinical years of training in medicine.

° ° °

DEDICATION CEREMONIES were held for Towner county's new $475,000 Memorial Hospital in Cando recently. The community's new 20-bed hospital is owned and operated by the Sisters of St. Francis of Hankinson, North Dakota. Sister Bernadine, the superintendent, is president of the North Dakota Hospital Association.

° ° °

DR. WILFRED E. BLATHERWICK, who has served the Reservation country for more than 30 years, is leaving Sanish to move to the Minnesota lake country, some 30 miles east of Brainerd.

ASHLEY, NORTH DAKOTA, turned out to honor Dr. C. C. Campbell for his 44 years of service to the community recently. The doctor plans to retire to be near his only son who lives in New York state. At the special program held in the high school auditorium, Dr. N. O. Brink of Bismarck gave the main address.

Minnesota

DR. A. B. BAKER, professor of neurology at the University of Minnesota, has been named chairman of the recently formed national committee for research in neurological and sensory disorders. At the annual meeting of the American Orthopsychiatric association Dr. H. S. Lippman was elected president of the organization for 1953-54.

° ° °

AT THE MAY MEETING, the University of Minnesota's Board of Regents approved the formation of the Owen H. Wangensteen Surgical Education Foundation which honors the head of the department of surgery. Purpose of the Foundation is to promote advanced surgical education, and Dr. Wangensteen will act as an advisor in the administration of the funds.

° ° °

DR. RUTH E. BOYNTON, professor, School of Public Health, and director, Students' Health Service, attended the annual meeting of the American College Health Association in Columbus, Ohio. She acted as moderator in a panel discussion on "Health Insurance Plans for Colleges."

° ° °

ONE of the five Macalester college alumni to be given "useful citizen" citations recently was Dr. Byron Cochrane, class of 1932, who practices in St. Paul.

° ° °

BATTLE-LINES for the 1953 fight against polio were drawn up by a group of Minnesota women in June when a conference of foundation leaders and committee chairmen was held in Minneapolis. Among the speakers were: Dr. Dean S. Fleming, director of the state division of disease prevention and control; Dr. Willis E. Dugan, state March of Dimes chairman, and Miss Jean D. Conklin, administrator, Gillette State Hospital for Crippled Children. One of the objectives of the conference was to make plans for providing communities with data for use in the event of a polio outbreak.

° ° °

TWO NOBEL PRIZE WINNERS appeared on the same platform as speakers at the Centennial celebration of St. Joseph's hospital in St. Paul. They were Sir Alexander Fleming, London, discoverer of penicillin, and Dr. Phillip Hench, Mayo Clinic, Rochester, co-discoverer of cortisone. Dr. Richard R. Trail, Papworth village, Cambridge, England, spoke on "Rehabilitation of the Tuberculous Patient." Dr. Trail is director of the 35-year-old village, a unique project in community relations where tubercular patients, discharged from a nearby government sanitarium, are given employment on a 6-hour workday basis.

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*Glazebrook, A. J.: Brit. M. J., 2:1328 (Dec. 20) 1952.

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REHABILITATION OF THE TUBERCULOUS

(Continued from page 274)

Altro in 1918, did not reach full day working capacity until 1923, and died of a "stroke" in 1943. In the twenty-five years at Altro, he had earned in wages over $30,000. He had been entirely selfsupporting for about twenty years; his children are grown and married, without other cases of tuberculosis developing.

About five years ago Dr. Norvin Kiefer, then with the U. S. Public Health Service, Tuberculosis Control Division, said "about 7.5 per cent of the dischargees from hospitals and sanatoria are good chronics." Chemotherapy is extending the lives of many of these patients. They can make a contribution. Neglected, they are a danger and a social and economic waste.

These persons affect hospital care both in quantity and in quality. Occupying hospital beds though not acutely ill, they deprive acute cases of needed care, or, if sent home without any constructive plans, they are prematurely thrown on the scrap heap and become a threat to the family and the community, socially and epidemiologically.

Drs. Heath and McDougall (Dr. McDougall is chief of the tuberculosis division of the World Health Organization) in their book "Rehabilitating the Tuberculous," say "Rehabilitation means restoration of the patient to the degree of economic security which will be within the limits of his physical resources."

Under a medically supervised program as in a sheltered workshop, many of these employable good chronics become partially or completely self-supporting, some graduating into industry.

A rehabilitation workshop not only serves clients, reduces relapses and enables patients to live useful, productive lives, but it is a demonstration center. Properly publicized, it helps improve public understanding and the attitude of employers, and has influenced some large employers in providing graduated work in industry.

CESAREAN SECTION AFTER ONSET OF LABOR

(Continued from page 279)

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THIRTY-TWO CASES OF RENAL GLYCOSURIA

(Continued from page 277)

CONCLUSIONS

1. The dividing line between true renal glycosuria and pseudo-renal glycosuria is less concise than is believed, and they probably are the same entity.

2. There is an entity in which the span of the glucose tolerance curve is normal, but the peak is high. This has a possible explanation in a slow, but adequate islet cell response.

3. One must rely upon an abnormal fasting blood sugar or a glucose tolerance curve in making a diagnosis of diabetes before starting treatment.

4. One must follow glycosurics of any type with the glucose tolerance curve in order to determine whether there is a change, for each is an individual case and one cannot cite statistics in determining his prognonsis.

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EDITORIAL

(Continued from page 299)

ment of the architects in the construction of this beautiful edifice, the founders, the community of Hudson and medicine generally will take as great pride in the achievement as will those more directly responsible for it. Rarely, if ever, does the Marseillaise of Victory ring in the ears of the originators and sponsors of great projects. There are always more hurdles directly ahead. While we express gratitude for the great tasks that have been completed, let us gird ourselves for the problems of tomorrow and wish the men and women who will direct the destinies of the Hudson Memorial Hospital, God speed!

Owen H. Wangensteen, M.D.,
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University of Minnesota

The Journal Lancet

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

Meningococcal Disease

A Review

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MENINGOCOCCAL DISEASE is unusual in that the causative organism is so widely distributed in the general population, and yet the disease is relatively infrequent in those who harbor the organism. Various aspects of the disease caused by the meningococcus as well as a group of cases of meningitis seen at the Minneapolis General Hospital are reviewed in this report.

ETIOLOGY AND EPIDEMIOLOGY

The meningococcus (Neisseria intracellularis) is a gram-negative diplococcus which is usually intracellular, although it may be found extracellularly. Meningococci are not immunologically homogeneous and a number of serological types have been distinguished. These types have been classified into two fundamental groups—Group I containing Types I and III which are closely related, and Group II made up of Types II and IV. There are other strains, not commonly found, which do not fall into these groups. A marked variation in the frequency of occurrence of the two groups is seen: in general, Group I is associated with the epidemic disease, while Group II is found more frequently in interepidemic years and among infants.[1]

The organism is found only in man. It is found in the nasopharynx in carriers, but on occasion has been isolated from the mouth, tonsils, oropharynx and anterior nares. All available evidence points to the dissemination of the disease by healthy human carriers via droplet infection. Because the organism dies quickly outside of the body, person to person transfer must be by intimate contact.[2] The association of the disease with crowded living conditions may so be explained. During nonepidemic times between 2 and 10 per cent of the population are found to be carriers, but during epidemics the proportion has been found to rise as high as 80 per cent.[3] The carrier aspects of this disease came into prominence during World War I when Glover[4] developed the doctrine that a carrier rate of 20 per cent or over in a community, was an index of overcrowding and a warning of an impending outbreak. Subsequently however, this impression has not been confirmed. Aycock and Mueller[5] from extensive studies in the U. S. Armed Forces during World War II, state "that it has become clear that the extent of the occurrence of the disease is by no means wholly a simple function of the prevalence of meningococcus carriers. Epidemics may occur in certain groups while other groups with the same carrier rate remain free of the disease, or the disease may change from sporadic to epidemic with no corresponding increase in the prevalence of the meningococcus in the same group." It becomes obvious that the development of meningococcal disease depends upon factors other than the presence of carriers. These are closely related to the varying virulence of the organism and the resistance of the host. A close relationship has been found between the Group I strains and major outbreaks. In the 1940-1942 epidemic in England, Harries[6] found

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that although Group II strains predominated in carriers, 90 per cent of the strains found in the spinal fluid in cases of meningitis belonged to Group I, suggesting that Group I strains are more virulent than those of Group II. However, the general experience has been that there is very little or no difference in the severity of the disease produced by these strains.

Most observers feel there must be a high degree of natural immunity to the disease since only few instances of more than one case of clinical meningococcal disease in the same family have been reported, and since only about 1 in 1,000 who have the organism in the nasopharynx develops disease.[7] The degree of immunity acquired after an attack is unknown but is presumed to be durable, and second attacks are very rare. The immunity of carriers is probably due to repeated exposure to meningococci of low virulence. The formation of antibodies as a result of the disease can be demonstrated by agglutination, mouse protection, precipitin reaction, complement fixation and bactericidal techniques. That some immunity is acquired is suggested by the decrease in attack rate with advancing age in civilian populations (except for the 15 to 25 age group) and the greater susceptibility of raw recruits in military populations.[7]

Meningococcal infection is primarily a disease of childhood. Banks,[8] from a series of 706 cases illustrated some general principles of age incidence: (1) there are far more cases in infants under one year of age than in any other single year of age, (2) the incidence declines with age, except for the period of 15 to 25 years; after age 35 there is a sharp drop and after 55 a still sharper drop. Levinson[9] states that 80 per cent of all endemic cases of meningococcal meningitis occur before the tenth year, the largest number occurring during the first two years of life.

During the period January 1947 to December 1951, 66 cases of proven meningococcal disease were admitted to the Minneapolis General Hospital (M.G.H.). Forty-three cases were under 16 years of age, 23 over. Only those in the age group under 16 were reviewed. The findings as to age incidence are as follows:

0 to 11 months	11 cases
1 year	8 cases
2 years	8 cases
3 years	5 cases
4 years	1 case
5 to 9 years	7 cases
10 to 16 years	3 cases

The disease may occur at any time of the year, but is more frequent during the late winter and early spring. Of the cases at M.G.H., most were found in February, October, March, January, in that order and at least one case was found in each month except August.

The incidence of meningococcal meningitis in the period reviewed was compared to that of the other purulent meningitides:

Meningococcal	41 cases
Influenzal	23 cases
Pneumococcal	4 cases
Undetermined etiology	21 cases

PATHOGENESIS

In the nasopharynx, the meningococcus leads mostly a saprophytic or semisaprophytic existence. Infection in this area by this organism may or may not be indicated by clinical disease, but usually is not. It is generally accepted[10] that there are three stages in the development of meningococcal infection: (1) localization in the nasopharynx, (2) invasion of the blood stream, (3) localization in various body tissues, particularly the meninges. The third stage develops when spontaneous resistance or treatment does not prevent it. Campbell[11] attempts to explain hematogenous spread by a phagocytosis of the meningococci in the nasopharynx, and then a breakdown of the phagocytes by the virulent meningococcic toxin liberating the organism into the blood stream. The old theory of direct spread of the infection from the nasopharynx to the meninges via the perineural sheaths of the olfactory nerves has been generally abandoned because of the significant evidence put forth in favor of the hematogenous theory.

CLINICAL FORMS OF THE DISEASE

Meningitis

The *ordinary form* of meningitis is usually encountered in about 90 per cent of the clinical cases during epidemics, and in over 95 per cent of cases during nonepidemic periods.[8] It is preceded or accompanied by a nasopharyngitis in about one-third of the cases, according to Banks. Bradford[12] states that approximately 50 per cent are preceded by upper respiratory infection. In the series at M.G.H., a history of nose and throat infection immediately preceding the onset of meningitis, was obtained in 24 cases or 58 per cent. Clinical findings of such infection on admission were found in 21 cases or 51 per cent. The role of the meningococcus in the production of nasopharyngitis is uncertain because the more common organisms of the respiratory tract obscure the picture. However, pure cultures have on occasion been obtained

in cases of tonsillitis and pharyngitis. Flack[13] showed that irrespective of the absence or presence of clinical nasopharyngitis, the same type of organism as that in the spinal fluid may be isolated from the nasopharynx within a day or two of the onset of symptoms of meningitis.

As is well known, the onset is sudden with fever, general malaise, headache, vomiting and signs of meningeal irritation. An early sign frequently is the appearance of the typical petechial or purpuric rash. Since the diagnostic criteria are not as likely to be present in infants as in older children, the cases from M.G.H. were divided into two groups, those over and those under two years of age. There were 18 under 24 months of age, and 23 over 24 months. The following physical signs were found on admission:

	Under 2 years *Number cases*	*Over 2 years* *Number cases*
Temperature 100°+	18	22
Stiff neck	17	21
Kernig	14	16
Brudzinski	11	16
Opisthotonus	3	5
Petechiae	6	15
Tense fontanelle	6	0
Coma	3	3
Papilledema	1	2
Babinski	3	1

There was considerable variation in the severity of the clinical picture, but most of the patients appeared critically ill at the time of admission. The average duration of symptoms prior to admission was 2.5 days. The shortest period was 12 hours, the longest 7 days.

The laboratory findings in the group were analyzed. Most of the spinal fluids showed a pleocytosis of over 1,000 cells, predominantly polymorphonuclear in type. The highest count was 53,000 per cu. mm., the lowest 186 per cu. mm. The protein was elevated in all but 2 fluids of 36 examined. Sugar was decreased in 21 of 36 specimens. Thirty-seven spinal fluids out of 41 examined showed meningococci on direct smear, while 31 specimens out of 40 cultured produced the organism. Of 36 blood cultures 9 were positive. Only 3 of 41 nose and throat cultures were positive for the meningococcus, probably due to the fact that these specimens were not routinely cultured for meningococci. Almost all the cases showed a leucocytosis over 10,000 per cu. mm.; the highest value being 57,000 per cu. mm. and the lowest 6,550 per cu. mm. Polymorphonuclear leucocytes generally predominated. Albuminuria was found in close to one-third of the cases but no significant urinary findings were observed consistently.

In the *mild and abortive forms* of meningitis, symptoms are vague and disappear usually within a day or two without any treatment. However, some cases do not clear spontaneously and may persist for several weeks until the diagnosis is made by lumbar puncture. These cases respond to proper treatment, but relapses and recurrences are not uncommon.

The *chronic form* of meningitis develops from the ordinary form when the latter has been unrecognized or untreated in the early acute stage. This type is almost unheard of in our present age of chemotherapy and antibiotic treatment.

Chronic Meningococcal Septicemia—Meningococcemia

Bacteremia may be mild to severe. It is very probable that during periods in which there is much meningococcal infection, some cases in which there is illness of a mild nature due to the meningococcus are not detected and these cases recover spontaneously without therapy.[14] In some cases illness is chronic, and the clinical picture is characterized by bouts of fever usually low grade, recurrent crops of skin lesions which often appear with the rise in temperature, and vague joint and muscle complaints. The diagnosis is usually made on blood culture. Before the advent of the sulfonamides, this condition sometimes persisted for months, and even years, before terminating spontaneously or ending in meningitis. MacLean[15] cautions that temptations to do spinal fluid examinations in patients with this syndrome without signs of central nervous system involvement, be rigorously repressed. In his experience this diagnostic procedure has been dangerous, for within 24 hours after lumbar puncture severe meningitis has on occasion ensued, perhaps due to inoculation of the fluid with the needle or by some change in the blood-brain barrier.

Fulminating Meningococcal Septicemia

The onset of fulminating septicemia is usually abrupt with high fever, chills, vomiting, and the rapid development of skin lesions. Coma and a state of shock are frequently seen. When meningeal signs occur they usually do so several days after the onset. Most of the cases in which meningitis does not occur run a rapidly acute course.

Banks suggests that sufficient correlation between organic damage and clinical symptoms has been demonstrated to justify the classification of fulminating meningococcal septicemia into three broad types: (1) *Encephalitic*— when central nervous system symptoms such as coma are present and there is no state of shock.

In such cases, he has found at autopsy congestion, edema, capillary thromboses and hemorrhages, and perivascular infiltration in the brain. (2) *Adrenal* – when there are signs of peripheral vascular collapse but the mental state is clear. Autopsy findings in these instances have been adrenal hemorrhages while pathology in the nervous system has been nil. (3) *Mixed or encephalitic adrenal* – when there are both coma and a state of shock. In one of the recovered cases of what Banks has called the adrenal type, a child who was normal at the time of illness at age six, was found to be suffering from pituitary dwarfism at age eleven. That author thinks that occasionally pituitary lesions are found with the adrenal type and has shown this in some of his autopsy studies.

Acute Diffuse Encephalitic Syndrome (Banks)

This condition is characterized by the development early in the course of meningitis, of a deep coma with no response to stimuli, and the presence of multiple neurological manifestations. It is often fatal in 3 to 7 days without any return of consciousness. The clinical picture has been correlated with findings at autopsy which are similar to those found in cases of the encephalitic type of septicemia. In addition, however, degenerative changes in the neurones are found as well as purulent meningitis. In patients who had been getting treatment the meningitis is noted to be improving. Supportive evidence of diffuse encephalitis is obtained from recovered patients, some of whom have had upper motor neuron involvement and transient Parkinsonism in convalescence.

Acute Focal Encephalitic Syndrome (Banks)

Such cases appear at first to be severe examples of the ordinary form of meningitis, and after one or two days begin to recover slowly. Recovery is interrupted by sudden collapse, coma and death. In cases that have displayed this clinical picture, focal vascular lesions in the brain stem and cervical cord have been found as well as chromatolysis of the nerve cells in these areas.

Rarer Forms

The attention diverted toward the lower respiratory tract in meningococcal infections has been minimal. Holm and Davison,[16] and Davison, Holm and Emmons[17] concluded that both lobar *pneumonia* and *bronchopneumonia* may be produced by the meningococcus; also, that meningitis may be produced from cases of pneumonia, and vice-versa. These authors made cultures from the lungs of 23 of their patients who died and found 7 pure cultures of meningococci and 16 mixed. Roberg[18] suggests that if sputum in cases of pneumonia be routinely cultured for the meningococcus, recognition of respiratory infection by this organism would be made more frequently. The pleura is seldom involved.[19] There are two cases in the literature of pleural effusion with pneumonia due to the meningococcus.[20,21]

Primary meningococcal conjunctivitis, characterized by a purulent conjunctivitis involving one or both eyes, has been reported about 30 times in the literature. There are no permanent eye sequelae. Cases of meningitis and sepsis may result from this syndrome.

Crawford[22] reports a case of *meningococcal hepatitis* which was treated with sulfonamides with a rapid fall in temperature to normal and disappearance of the jaundice.

THE CUTANEOUS LESIONS IN MENINGOCOCCAL INFECTION

The occurrence of skin lesions in various series has varied up to 100 per cent in an epidemic. In the M.G.H. group 50 per cent of the cases of meningitis and both of the two cases of septicemia were found to have petechiae. During epidemics there is greater consciousness, and this probably promotes the finding of a greater incidence of rashes.

The skin lesions may assume a wide variety of patterns which include erythematous macules, papules, nodules, petechial and purpuric lesions, vesicles and pustules. Some observers consider the maculo-papular rash as prodromal. The extremities and regions of the body subject to pressure are the commonest sites and petechiae are frequently found in the conjunctivae and mucous membranes. The face, palms and soles are usually spared. Nodular lesions may resemble those of erythema nodosum. Sometimes the lesions may be tender. Herpes simplex is common, occurring usually about the second day of the disease. No herpes was reported in our series. Maculo-papular lesions have been found to fade in a few days even if no therapy has been used and within one day if penicillin or sulfonamides are used. The hemorrhagic element is not influenced by the aforementioned agents; it involutes slowly over a period of from several days to weeks. Necrosis and sloughing of purpuric lesions may occur.

Numerous observers have reported finding meningococci in the petechial and purpuric skin lesions. In many cases of fulminating septicemia, meningococci may be demonstrated in a smear of the peripheral blood. Hill and Kinney,[23] from a histological study of 25 necropsies explain the

cutaneous rash on the basis of vascular damage by the meningococcus. The sequence of events is considered to be as follows: (1) the localization of the organism in the endothelium, (2) endothelial damage and inflammation of the vessel walls, (3) resultant necrosis and thrombosis, (4) extravasation of red cells due to these changes. Similar vascular lesions are found on the serous surfaces in the body and in the lungs, liver, spleen, kidney and intestines. The platelet involvement in the thrombi and the resultant thrombocytopenia may add to the increased hemorrhagic tendency. Vascular thrombosis has been found in some cases to be severe enough to produce gangrene of a limb.[24]

THE WATERHOUSE-FRIDERICHSEN SYNDROME

The Waterhouse-Friderichsen syndrome was described by the earlier authors as an acute febrile illness, characterized by the sudden development of a state of shock, hemorrhagic skin rashes, early fatal termination and by the finding of adrenal hemorrhages at post mortem. The syndrome was first described by Voelcker[25] in 1894, and this was followed by Waterhouse[26] in 1911 and Friderichsen[27] in 1918. The cause of the disease was not discovered in any of the cases reported by these authors. In 1916, Maclagan and Cooke[28] first reported this syndrome in association with meningococcal meningitis. In almost all instances the syndrome is caused by meningococcal infection. Other organisms such as the staphylococcus, streptococcus and pneumococcus have however occasionally been found to be responsible.[29,30]

Lindsey[31] states that 90 per cent of the known cases have occurred in children under the age of nine years. There was one case in the M.G.H. series, in a male infant 13 months of age. This patient had a typical acute onset of fever, lethargy and a petechial rash 12 hours before admission to hospital. When first seen, he had a temperature of 105°, a widespread petechial and purpuric eruption, and was in both coma and shock. His condition deteriorated rapidly and death ensued three hours after admission. Laboratory studies revealed a positive blood culture and a negative spinal fluid. At autopsy, hemorrhages were found in both adrenals, in the kidneys, and on the serosal surfaces.

Bernhard and Jordan,[32] in a review of 214 cases of meningococcal infection report an incidence of 3.3 per cent of this syndrome; Kinsman[33] and his group of cases report an incidence of 2.2 per cent. Daniels[14] reviewed the post mortem findings of 300 soldiers who died with meningococcal infection and found that 42 per cent of these had adrenal hemorrhages. However, he also noted there were four cases which presented clinical manifestations of the syndrome but had normal adrenals. The analysis of the degree of adrenal hemorrhage to the duration of life, indicated that patients with massive hemorrhage die most rapidly.

Rich[34] and Kinsman examined a number of adrenals without gross hemorrhage from patients who had the clinical findings of the syndrome, and uniformly found microscopic cellular damage. Both these workers found degenerative changes consisting of disruption of the cortical cords, death and lysis of cells and congestion and edema of the stroma, involving the entire reticular and the inner half of the fascicular zone. Kinsman attempted to correlate the pathological findings with the clinical picture, and concluded that the clinical course of the patients presenting the degenerative lesions was not essentially different from that of patients showing the hemorrhagic changes. It is his belief that "these two types of changes are stages in the same process, the first representing an early, probably still reversible phase and the latter the terminal irreversible phase."

The cause of the circulatory collapse in this disease has been subject to much speculation. Thomas and Leiphart[35] and Kinsman believe that the shock is due primarily to the widespread tissue changes and hemorrhages rather than solely adrenal insufficiency because of hemorrhage and degenerative changes. It is their opinion the adrenal lesions play a part, but only a part. If the adrenals do play a big role in the production of collapse it may well be that those cases which have recovered have had those degenerative changes in the adrenal that Kinsman feels are reversible. Marangoni and D'Agati[36] feel that there are two stages in the Waterhouse-Friderichsen syndrome – (1) the phase of profound shock and circulatory collapse, and if this is survived (2) the hepato-renal phase characterized clinically by oliguria with azotemia and pathologically by severe central necrosis of the liver associated with changes in the glomeruli and tubules of the kidney. This impression is based on two patients with long survivals of 80 and 88 hours.

Very little study has been made of the blood chemistries in this disease. Azotemia is found in most cases due to the effect of dehydration and collapse on renal function. Hypoglycemia has been observed frequently, and is believed to be secondary to adrenal cortical damage.[37] Most workers have found the sodium, chloride and

potassium levels to be normal or only slightly changed, but some have found increases in potassium with decreases in sodium and chlorides. It is suggested that the alterations in renal function secondary to dehydration and shock tend to conserve the electrolytes and so we frequently do not see the true values of adrenal insufficiency.[38]

The discussion of this facet of meningococcal disease was started by using the description of the original observers. The only common denominator in their cases was massive adrenal hemorrhages seen at post mortem. Since there have been patients who have survived with this clinical picture and also those who have had this clinical picture but no adrenal hemorrhage at autopsy, it follows that the diagnosis of Waterhouse-Friderichsen syndrome is essentially a pathologic one and should be used only for those cases in which adrenal hemorrhages are demonstrated. Many suggest that the term "Waterhouse-Friderichsen syndrome" be abandoned entirely or else be rigidly restricted. These cases should properly be classified as acute fulminating septicemias.

COMPLICATIONS AND SEQUELAE

Since the advent of chemotherapy complications and sequelae have been considerably reduced but they still do occur. Hoyne[39] for example, found an incidence of 23.3 per cent complications in his series of 727 cases which were treated since the introduction of sulfonamides and penicillin.

Arthritis is considered at the present time to be the most common complication. Hoyne found an incidence of 9.6 per cent while others have found the frequency to be about 4 per cent.[8] Occasionally this is found before the onset of meningitis, due to the septicemia. Joint involvement is usually found during the first week of the disease and more commonly involves the larger joints although the joints of the fingers, toes and wrist may be affected. The joint becomes swollen, tender and inflamed. The fluid is usually serous but may be turbid and sometimes meningococci can be cultured from the aspirated fluid. Inflammation usually subsides in a few days, but resolution may take as long as several months. If the arthritis is destructive it may produce ankyloses and other deformities.

Suppurative otitis media early in the disease is not infrequent. Due to the infection of the perilymph via its direct connection with the subarachnoid space, *labyrinthitis* may occur. Both the vestibule and cochlea are usually affected. Permanent *deafness* may result due to a degeneration of the auditory nerve from damage to the organ of corti. Such damage occurs early in the disease and therefore recovery is not frequent even with prompt chemotherapy. Banks found the incidence of labyrinthitis to be 4 per cent.

Cranial nerve paralyses are probably due to pressure of the exudate in the subarachnoid space on the nerves as they emerge from the brain stem, or else they may be accounted for by a toxic neuritis. The nerves most commonly affected, in order of frequency are VI, VII, III and IV. The duration of the paralysis has been observed to vary from several days to as long as several months, but it always clears up completely. *Cortical damage* may occur secondary to an encephalitis or pressure on the cortex from the subarachnoid exudate early in the disease. This may produce convulsions, generalized or focal, hemiplegia, spastic paralyses and mental changes. Convulsions may usher in the disease, but after the onset are unusual. *Neuritis, radiculitis, myelitis* can occur due to extension of the infection into the cord parenchyma or secondary to pressure effects. *Hydrocephalus,* produced by adhesions in the subarachnoid space, was a very common complication in the presulfonamide era but now is quite rare.

Eye complications include *uveitis, choroiditis* and sometimes a *panophthalmitis,* which are usually embolic in origin, frequently unilateral and may lead to permanent destruction of the eye. *Optic neuritis* may occur, and also *conjunctivitis.*

Endocarditis may be seen in a fulminating septicemia. *Toxic myocarditis, pericarditis* and *pericardial effusion* may occur. Pericarditis is a late complication and because of the reduction in mortality in the early stage of this disease by chemotherapy has been reported more frequently in recent years. It is rare in adults and only one case in a child has been reported.[40] *Pneumonia,* due to meningococci or secondary invaders, *pleurisy, and empyema* have been reported.

In the M.G.H. series 15 patients were noted to have complication, an incidence of 35 per cent. These are tabulated as follows:

1. C.N.S. — a)	Paresis Cranial Nerves		4 cases
	N VI	2	
	N VII	1	
	N VI + VII	1	
b)	Convulsions		8 cases
	Pre-admission	7	
	Post-admission	1	
2. Arthritis			2 cases
3. Cardiovascular			2 cases
a)	Toxic myocarditis	1	
b)	Pericarditis	1	

One of the patients included above had convulsions and a cranial nerve paresis combined.

TREATMENT

There have been three distinct periods in the treatment of meningococcal disease. Before 1900, the treatment was symptomatic and supportive, and the fatality rates were from 70 to 90 per cent. The second period from 1900 to 1936 saw the introduction of specific serum therapy and the rate dropped to 45 to 50 per cent. In 1936, with the introduction of chemotherapy, the present period began and the rate has dropped to from 0 to 15 per cent.

Sulfonamides were the first of the new agents to be used in treatment. Schoenbach and Phair[41] showed that in vitro 98.1 per cent of 430 meningococcal strains were inhibited by 0.5 mg. per cent of sulfadiazine. Because of the efficacy of the sulfonamides many observers feel that these agents by themselves are sufficient antibacterial therapy. Hoyne treated patients with different sulfonamides and found there was only slight difference in the therapeutic efficiency of the various types. High blood levels may not be an essential requirement for the efficient treatment of this disease.

The routine dosage schedule of 1 grain per pound per day is adequate. During the first 24 hours of therapy it may be best to use between 1.5 and 2 grains per pound. Then the dosage should be dropped down to 1 grain per pound for maintenance. There is general agreement that the drug should be given intravenously in a 5 per cent solution for at least the first dose and subsequently until the patient is able to take the drug by mouth. Sulfonamides may be given subcutaneously in a similar solution until the acute phase is over.

Because of the high frequency of renal complications, from 8 to 50 per cent in different reports, it has been suggested that mixtures of sulfonamides be used to reduce this incidence. Ziller and his associates,[42] however, feel that the disadvantages of using the mixture outweigh the advantages. In their experience no significant difference was found in fatality rates or incidence of renal complications, but a much higher incidence of drug fever and rashes was observed when a mixture was used than when one sulfonamide was used alone. Gantrisin has been used with adequate results and no complications.

There is at present a great deal of uncertainty with regard to the duration of chemotherapy and the total amount of drug required in each case. The average length of time Hoyne's patients were on sulfas was 8.3 days but in many cases he found 5 days sufficient. Kaufman[43] and associates suggest that therapy may be safely discontinued after the patient has been afebrile for 24 to 48 hours and has received a total of 15 to 20 grams of the drug. They find it unnecessary to use more than that amount of sulfadiazine in the average case, although they admit an occasional case may require more.

Penicillin has been found to inhibit in vitro about 98 per cent of strains of meningococci when the level is 0.1 to 0.5 units per cc. Controlled series[8] have shown that penicillin is inferior to sulfonamides in the treatment of meningococcal meningitis. Lohrey and Tomey[44] from a series using penicillin alone concluded the results were not of sufficient value to warrant the use of penicillin as a form of treatment of this disease when simpler and more effective agents as the sulfonamides are available. Hoyne is not convinced that patients treated with both sulfonamides and penicillin respond more rapidly than those treated with sulfas alone. However, he is of the opinion that penicillin is of use in eye complications. Scherling and Platou[45] suggest a combination of penicillin and sulfonamides is best.

Aureomycin and Chloromycetin have been shown to be quite effective in therapy. However, they are no more effective than sulfadiazine.

Treatment of the patients in our series of meningitis was variable. In only one patient was one drug alone used, and that was aureomycin. The following combinations were used: Sulfadiazine and penicillin, 31 cases; sulfadiazine, penicillin and streptomycin, 5 cases; sulfadiazine, penicillin and Chloromycetin, 1 case; sulfadiazine, penicillin and aureomycin, 3 cases. The response to therapy was good in almost all cases. Two patients did not respond and died within 24 hours after admission.

Response to efficient sulfonamide therapy is dramatic. Usually striking clinical improvement is seen by the second or third day of chemotherapy. Fever drops rapidly by lysis or crisis and there is progressive improvement. Subsequent temperature elevations usually are indicative of drug reaction or the development of a complication. It is commonly accepted that it is unnecessary to resort to lumbar puncture for the purpose of evaluating the progress of a case. The cerebro-spinal fluid is nearly always sterile after 12 to 24 hours of efficient sulfonamide therapy. Of course, in those instances in which the course of the disease is unclear or the cause

of a persistent fever is not apparent, a lumbar puncture is indicated.

The treatment of fulminating meningococcal septicemia is a challenge. Infection should be combated with sulfadiazine. Penicillin may be used in addition. To prevent anoxia, oxygen should be given. Adrenalin, adrenal cortical extract and plasma have been used in the past to combat shock without much success. Cortisone may be more useful because it is much more potent in overcoming stress than adrenal extracts. Recent reports of the use of cortisone are encouraging.[46,47,48] To date, no one has determined the dose of cortisone necessary for treatment. Hodes, Moloshok and Markowitz suggest that the total blood eosinophil count as a test of adrenocortical function may be useful as a guide in the prognosis and treatment of meningococcal infection.[46]

PROPHYLAXIS

The carrier state of a group has been shown to have a complex ever changing pattern. It therefore seems useless and unnecessary to try to isolate carriers and to quarantine contacts. Mass prophylaxis has been attempted in well controlled situations with a significant drop in the carrier rate and decreased incidence of the disease.[49] Prophylaxis may therefore be of value in a controlled situation such as an orphanage, special schools and institutions in general. However, prophylaxis has little value in the case of a family, since its members unless isolated from the rest of the community quickly become reinfected. Caution must be exercised in the prophylactic use of sulfonamides because the administration of small doses to a large population over a long time may result in favoring survival of drug resistant strains.

The convalescent rarely harbors the organism since sulfonamides are so effective. The organism is very sensitive to its environment outside of the body and quickly dies. Direct infection is extremely rare. Therefore, the routine use of isolation technique in the acute phase may be generally impractical and unnecessary. However, isolation technique for a short time probably is advisable when one is exposed to gross infection by very close contact with the patient.

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The Diagnosis and Treatment of Proctologic Disorders*

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Why does the patient with a proctologic disorder come to a physician? The two most common complaints which bring the patient to see the doctor are pain and/or bleeding from the rectum. Next in frequency probably would be pruritus, protrusion or a persistent discharge which either is irritating or persistently soils the patient's clothing.

I believe I am safe in saying that more than fifty per cent of diagnoses can be made by taking a very careful history from the patient, assuming, of course, that the patient is of average mentality and exhibits some degree of cooperation in giving a history. Adequate physical examination will usually serve to confirm the tentative diagnosis which has been arrived at in the history and to uncover any associated pathology which might exist. The average proctologic patient when asked what is troubling him will reply, "I have piles, doctor," or make some similar remark. When asked, "How do they trouble you?" a variety of answers is forthcoming. The patient with a primary complaint of protracted pain may or may not have hemorrhoids but chances are his symptom of pain is probably not from his hemorrhoids but from a fissure; short duration pain is usually from an external thrombosis, an abscess or an acute tear in the anal canal.

Careful inquiry into the type of pain, mode of onset and duration will often lead to the correct diagnosis even before examination is made. The typical story of a fissure is a sharp burning pain which comes on with a hard stool and lasts for varying periods after the bowel movement. When the patient cleanses himself he will often note a small amount of bright red blood on the tissue. The pain gradually subsides and may go away completely until the next stool. An external thrombosis on the other hand will have a more gradual onset over a period of a few hours either after straining at stool, on lifting heavy objects or it may even follow a bout of diarrhea. The pain gets worse as time goes by and the patient notes a swelling which he will describe when asked. These patients are usually more comfortable standing than sitting. Perianal abscesses begin wth a dull, gradually increasing pain and tenderness for a day or two or several days. These occasionally are associated with chills and fever. The fever is more pronounced with staphylococcus and streptococcus infections. Abscesses begin with diffuse induration and only in the late abscess which is pointing is localized swelling observed. The patient will often complain of a full feeling in the rectum.

Bleeding from the rectum is a very significant symptom which should never be disregarded and not taken lightly. No patient who has ever passed blood from the rectum should be denied the benefit of a thorough proctosigmoidoscopic examination. When we realize that about 75 per cent of malignant lesions of the rectum and colon are within reach of the 25 cm. proctoscope it goes without saying that this simple examination should be done with much greater frequency than is usually the case. It should probably be part of a regular periodic physical examination.

If any blood has been noted by the patient careful and persistent inquiry should be made as to the amount of blood, whether it is bright red or old, if the blood is mixed with mucus and is there any pain associated with the bleeding. *The fact that there has been any bleeding should be reason enough not to give up until all resources to find the source have been exhausted.*

One should remember that small amounts of bright red blood which are associated with pain on passage of stool are most likely due to fissure. Large quantities of bright red blood passed with or after stool and not associated with painful defecation are most likely from vascular in-

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ternal hemorrhoids. Old blood or blood clots can be due to hemorrhoidal bleeding but most frequently come from a neoplasm or lesion higher in the rectum or colon. Blood mixed with mucus is often primafacia evidence of either a polyp or a malignant lesion somewhere in the bowel and I feel that this one finding is enough indication for barium enema and air contrast studies of the colon. If the proctoscopic examination shows chronic ulcerative colitis these procedures can be dispensed with. Careful inquiry into the patient's history regarding localized abdominal pains, abdominal cramps, changes in bowel habits and weight loss are rewarding in helping to rule out the presence of intraabdominal pathology. These are often late signs of colonic lesions and ideally should not have supervened before a diagnosis has been established. There are, however, some of the annular constricting carcinomas which do not ulcerate and bleed where the first symptoms are those of bowel obstruction. The obstruction may be complete and acute or partial with recurrent cramps and persistent progressive abdominal distention.

The technique of a good proctoscopic examination is most important. First of all it should be a relatively painless operation. The patient, of course, appreciates not being hurt and it is also much easier to visualize the pathology if the patient is well relaxed. In our practice, we use a topic anesthetic, 4 per cent cocaine in lubricating jelly, to anesthetize the anal canal, and find it completely adequate if two or three minutes are allowed to elapse after application of the jelly. With this anesthesia it is possible to examine even the patient with an acute fissure or an external thrombosis.

Inspection of the anus reveals such things as external openings of fistulas, sentinel piles at the apex of a chronic fissure, external thromboses and the perianal irritation of pruritus. The appearance of the skin is often a good guide as to the type of topical application which will be the most effective in the relief of the pruritus. Mild applications should be used in acute cases. More stimulating applications in chronic cases. Most physicians make the mistake of using too strong solutions or ointments. It has been our experience that most cases of pruritus are overtreated with topic treatments. Good diet, to eliminate irritants, an astringent rectal irrigation and a mild topic application usually will clear up the pruritus if the physician and patient are persistent in the treatment.

A digital examination should be more than just putting a finger into the patient's rectum, for it often reveals information which cannot be gained even with speculum examination. The anal canal should be carefully palpated for spasm, stenosis and areas of scar. The size and thickness of sphincter muscle should be noted and of course careful search should be made for areas of induration where fistulas are suspected. This is best done by palpating the tissues between the thumb and forefinger. Any palpable tumor masses within the rectum should be palpated for fixation to the muscularis and other structures in the pelvis. After these procedures the anal canal and lower rectum can be visualized with a speculum and the choice of speculum is up to the physician. Needless to say, any patient with anorectal pathology should be examined with the sigmoidoscope to be sure that no associated pathology exists higher up. The Ives speculum is quite satisfactory for most cases where no stenosis or abnormal anal spasm exists. In cases with acute fissures, anal spasm or anal stenosis a smaller speculum such as the small Brinkerhof is more satisfactory. Ordinarly the bivalve speculum like a Pratt will cause too much pain for satisfactory examination. We feel that a proximally lighted sigmoidoscope is preferable to the distally lighted instrument because small bits of stool and mucus obscure the distal light and make the examination more difficult. The distally lighted scopes also have a much more delicate lamp which is more easily broken or burned out.

Ideally, a patient should be examined before and after enemas. Very frequently the only sign of a silent lesion above the 25 cm. level is a small amount of blood or blood-tinged mucus on the bowel wall. Conversely, there are times when an enema will stimulate some bleeding and bring down some blood or blood-tinged mucus from a high-lying lesion. The finding of any blood or bloody mucus indicates that barium enema and air contrast studies should be done.

I should like to emphasize the importance of expert x-ray studies. The constricting carcinomas are usually demonstrated even by those uninitiated in x-ray technique and interpretation, although they may sometimes be missed if the bowel is poorly prepared and not quite free of fecal material. However, the small polyps and polypoid carcinomas often defy even the most expert radiologist. We have had air contrast studies with new techniques where the radiologist localized and described polyps as small as 5 mm. in diameter. When a polypoid lesion is demonstrated above the 25 cm. level repeat studies should be done to be sure that it again

localizes in the same area before laparotomy is done. In this way unnecessary abdominal operations can be avoided. It is also important to not hesitate in ordering a repeat study when the first study is negative and the sigmoidoscopist suspects a lesion above. Whenever there is evidence of bleeding from above in sigmoidoscopic examination it is the duty of the radiologist to find the bleeding point and it also is the duty of the referring physician to insist that he make a thorough search for a lesion to explain the bleeding. We are all too eager to get a negative x-ray report and often we tend to forget that the radiologist can make mistakes the same as we do. There is an occasional patient with a polyp of the colon who even in the best hands requires two or three studies before the polyp is demonstrated. Unless the proctologist insists on the repeated examinations this polyp might well go on to malignant degeneration and metastasis before any significant symptoms bring the patient back to the physician. It goes without saying that adequate preparation of the bowel must be carried out before x-rays are made. A negative report on a bowel with any stool in it is, in my opinion, more dangerous than no x-ray, for it lulls both patient and physician into a sense of false security.

The treatment of proctologic conditions occupies volumes of medical literature which many of you have read so I shall try to point out a few of the principles of treatment of the various disorders. In doing anorectal surgery it is imperative that all the pathology be corrected and this should be easy provided the diagnostic principles have been carefully observed.

What constitutes a good hemorrhoidectomy? A good operation for hemorrhoids is one which removes all of the varicosities, does not leave the patient with too much scar tissue in the anal canal and leaves the patient with an outlet large enough to accommodate a constipated stool without cracking and becoming painful. In addition the patient should be left with good control. These same principles apply to all anorectal surgery. To accomplish these things one should not remove too much of the anoderm but still must make enough incisions to destroy all the vessels. The dissection type of hemorrhoidectomy popularized by Dr. Walter A. Fansler is in my opinion the best operation to accomplish this with the least danger of complication. I might remind you that many patients with a short anal canal and large hemorrhoids may have quite marked redundancy of the rectal mucosa above the hemorrhoids and unless this is excised the patient may later develop partial prolapse of this mucosa and feel that he has had recurrence of the hemorrhoids.

In treating the patient with chronic fissure-in-ano surgically it must be remembered that probably the main reason the fissure does not heal is that some degree of anal stenosis exists—either congenital or as a result of scarring from previous anorectal surgery or from the chronic fissure itself. Unless this stenosis is corrected, excision of the fissure will only be followed by recurrence and further difficulty as soon as a large hard stool is passed. Avulsion of the sphincter is often associated with hemorrhage into the sphincter and this is followed by fibrosis which causes even greater contracture of the anal canal. It also makes the anal canal inelastic and easily subject to further cracking. Partial incision of the external sphincter, posteriorly, at its point of insertion into the anococcygeal tendon in the midline to convert the anal canal into an inverted funnel instead of a cylinder is far more satisfactory. Great care must be exercised not to incise too deeply and render the patient incontinent of stool or gas. This is the reason for the great importance of observing the amount of sphincter muscle during the digital examination. There is an amazing variance in the amount of muscle in various individuals and what constitutes adequate incision in one will render another totally incontinent. There is no rule of thumb to follow in this situation. Only care and experience will indicate the answer in any given situation.

Fistula-in-ano and perirectal abscesses can be discussed together because nearly all perianal abscesses are fistulas as soon as they are drained. Good adequate drainage for perirectal or perianal abscess should be established as soon as the diagnosis is made. Cruciate incision and removal of a portion of the "flaps" is the best principle of treatment. "Scalp" the abscess carefully and leave a large enough wound – flat rather than deep – so it will heal from the bottom upwards without packing. Treatment with antibiotics in the hope abscesses will absorb is only waiting for further tissue destruction and extension of the abscess cavity. Delay is the cause of horseshoe fistula. The pus from one side burrows underneath the anococcygeal tendon and involves the other fossa. Incision and scalping is best done under general anesthesia in a hospital. The abscess should be widely saucerized to create as nearly flat a wound as possible and careful search for the internal opening should be made. The entire tract should be excised and saucerized. If saucerization of the tract destroys too

much of the sphincter mechanism then a heavy silk suture should be placed loosely around the sphincter and the muscle divided later when there is enough contracture of the cavity to prevent wide retraction of the divided ends. Many cases of anal incontinence can be prevented by this simple maneuver. In the postoperative treatment of these fistulas care must be exercised to be sure that they heal by granulation from the base of the wound to prevent pocketing of exudate and recurrence of the fistula. Complicated fistulae with multiple openings require the same principles of operation and general care as simple ones. Occasionally multiple stage operations may be necessary to effect a complete cure and still leave the patient with a functional anus.

All polyps of the rectum and colon should be removed. The method of removal and the extent of removal depends entirely upon the type of polyp, its location and number and distribution of the polyps. It is agreed that they are premalignant lesions so their presence is adequate indication for removal. Most pedunculated polyps within reach of the proctoscope can be removed by fulguration and single polyps above the reach of the proctoscope by incision of the bowel and polypectomy or segmental resection depending upon the size and character of the polyp. The presence of three or more polyps in different portions of the colon usually demands subtotal colectomy. This generalization can be modified in certain instances such as old, poor risk patients, long pedunculated polyps or complications which would make the risk of colectomy too great.

In treating carcinoma the only adequate treatment for a carcinoma of the rectum or colon is complete removal of the tumor and all of the adjacent lymph node bearing tissue. For carcinoma below the peritoneal reflection one stage abdominal-perineal excision gives the largest percentage of permanent cures. For tumors above this area "sphincter saving" operations may be considered but such operations should be advised cautiously. A good many chances of permanent cure are being sacrificed due to the present craze for "sphincter saving." Our only present hope to increase the cure rate for carcinoma of the colon and rectum is in earlier detection of the lesions and less delay in the treatment after the lesion has been discovered.

In brief summary, in proctologic conditions, as in any disease, the ancient principles of careful and complete history and good thorough physical examination cannot be overemphasized. I am reminded of Ferguson's Textbook of Ambulatory Surgery, in which the author points out that all that is needed to do a rectal examination is an eye, a finger, a finger cot and a rectum. In addition to these I should like to suggest a 25 centimeter proctoscope and a rectal speculum. If these articles are all used properly we can expect to see more diagnoses of both benign and malignant lesions of the anus, rectum and colon before they are inoperable or severe complications have supervened. Usually patients are not anxious to have rectal examinations but all patients who have anorectal pathology are grateful when it is discovered and corrected. It is the duty of the physician to do adequate rectal examination whenever a complete physical is done.

> It is the business of the physician to know, in the first place, things similar and things dissimilar; those connected with things most important, most easily known and in any wise known; which are to be seen, touched and heard; which are to be perceived in the sight, and the touch, and the hearing, and the nose, and the tongue, and the understanding; which are to be known by all means as we know other things.
>
> Hippocrates, *On The Surgery*

Observations on Some Hematological Effects of Cobalt-Iron Mixtures*

ROBERT J. ROHN, M.D. AND
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CONSIDERABLE DATA have been accumulated on the hematological effects of cobalt in experimental animals[1–6] and in humans.[7–16] While some of the published reports are contradictory, there is considerable uniformity of opinion that cobalt in sufficiently large dosage is a potent stimulus to erythropoiesis and hemoglobin formation. Surveys of the literature indicate that no author has reported any cobalt effect on leukocytes or thrombocytes in humans, although Valerio observed leukocytosis and doubling of platelets in guinea pigs on cobalt therapy.[6]

The mechanism by which cobalt salts induce erythremia is but poorly understood. Some authors[2,8,9] postulate that cobalt by interfering with cellular enzymes causes hematopoietic tissue hypoxia with resultant secondary erythremia. It has been shown that concomitant administration of ascorbic acid, methionine, choline, and vitamin B may interfere with the erythrogenic effects of cobalt.[14] Weissbecker,[14] however, states that such inhibition is only a first phase reaction, and that a second phase "true polyglobulism" is not affected by the use of such agents.

Levey[5] found that cytochrome C was ineffective in altering the effect of cobalt on erythropoiesis.

Davis et al[4] noted a two-phase effect of cobalt on erythropoiesis in ducks. In the first phase they observed a marked hyperplasia of the marrow. There was actual marrow hypoplasia, in the second phase, but there was also marked diminution in erythrophagocytosis so that erythremia was maintained.

Kato[7] is of the opinion that cobalt acts as a catalyst in stimulating erythropoiesis.

The use of cobalt salts has been advocated in the treatment of "idiopathic" hypochromic anemia,[11] anemias associated with chronic infections and malignancies,[9] hemolytic anemias,[10] and the anemias of infancy and childhood.[7,15]

Toxic reactions to cobalt therapy are not severe, and are usually troublesome only after parenteral therapy or in oral dosages exceeding 300 mg. per day. Toxic reactions consist of anorexia, nausea, vomiting, gastrointestinal burning, diarrhea, vasodilatation and faintness.

MATERIAL

To study the hematopoietic effects of cobalt in humans with anemia, 23 infants with iron deficiency anemias were carefully selected from the wards of the James Whitcomb Riley Hospital for Children. They ranged in age from one to 24 months. Although some of them were admitted to the hospital because of mild infections, they were not accepted for this study until such infections had completely cleared. Thus, in these patients, as far as we could determine, we were dealing with pure, iron deficiency anemias. By so limiting our patients we obtained a fairly homogeneous group with, presumably, highly reactive marrows. Another advantage in employing this group was the elimination of such variables as blood loss, infections, metabolic disorders, and neoplasms. The effects of cobalt-iron mixtures on nutritional iron deficiency anemias of infancy are briefly summarized in table I.

Because of some hematological effects which we observed in these iron deficiency anemias, we employed cobalt chloride in the treatment of three patients with marked marrow hypoplasia. These three patients will be discussed separately.

METHODS

All patients received thorough clinical examinations with appropriate laboratory examinations before being referred for this study.

In any patient in whom the hematological diagnosis was in doubt a bone marrow aspiration biopsy was obtained and studied with supravital and Wright's stains. All marrow specimens were cultured for Histoplasma capsulatum.

Repeated complete blood counts including

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TABLE I

RESPONSE OF 23 CASES OF IRON DEFICIENCY ANEMIA OF INFANCY TO COBALT-IRON THERAPY.

Case	Age in Mos.	Complicating Illness	R.B.C. Increase per day	Hgb. Increase per day	Reticulocyte Peak and Occurrence	Platelets Maximum Increase	Eosinophilia Peak Value	Basophilia Peak Value
1	1	Neonatal Jaundice	40,000	0.08 gm.	9% 10th day	1,600,000	12%	None
2	3	None	113,000	0.22 gm.	5.2% 9th day	None	None	None
3	17	None	74,000	0.15 gm.	6% 2nd day	800,000	None	None
4	5	Acute Laryngo-Tracheitis	−500	−0.01 gm.	4% 12th day	None	None	None
5	10	None	79,000	0.22 gm.	6.6% 7th day	None	6%	3%
6	15	None	133,000	0.20 gm.	16.5% 2nd day	None	10%	3%
7	3½	Infantile Diarrhea	19,000	0.03 gm.	3.4% 2nd day	1,300,000	None	None
8	11	None	26,000	0.07 gm.	9.4% 4th day	None	None	None
9	17	Herpetic Stomatitis	100,000	0.11 gm.	6% 3rd day	None	34%	5%
10	9	None	159,000	0.11 gm.	4.5% 5th day	2,250,000	10%	3%
11	14	None	155,000	0.14 gm.	10.7% 4th day	2,700,000	22%	18%
12	12	Cervical Lymphadenopathy	165,000	0.12 gm.	6% 12th day	6,300,000	16%	None
13	15	None	68,000	0.10 gm.	9% 3rd day	1,400,000	13%	4%
14	13	None	190,000	0.28 gm.	23% 4th day	500,000	None	None
15	6	Gastro-Enteritis	198,000	0.16 gm.	8.2% 7th day	1,000,000	15%	None
16	9	None	42,000	0.09 gm.	7.9% 5th day	4,200,000	16%	4%
17	24	None	81,000	0.16 gm.	10.6% 5th day	1,600,000	None	3%
18	19	Fever	78,000	0.15 gm.	8% 12th day	800,000	24%	4%
19	7	Urinary Infection	134,000	0.10 gm.	8.2% 16th day	2,700,000	19%	12%
20	24	None	122,000	0.15 gm.	12.3% 10th day	1,000,000	15%	None
21	16	Staphylococcal Adenitis	77,000	0.07 gm.	4% 13th day	1,900,000	16%	6%
22	12	None	107,000	0.15 gm.	4.5% 10th day	1,640,000	7%	None
23	15	None	134,000	0.10 gm.	12.2% 3rd day	900,000	12%	5%

hemoglobin, total erythrocyte, total leukocyte, platelet, and reticulocyte counts were obtained on all patients. All hemoglobin determinations were made with a carefully standardized Leitz photometer. All platelet counts were made using Damashek's method in which a special solution of brilliant cresyl blue is employed, and the number of platelets per 1000 red cells is counted. Normal values for this method range from 500,000 to 1,000,000 platelets per cu. mm. of blood. Reticulocyte counts were made simultaneously on the same preparations. Hemoglobin determinations and all total cell counts were made by our special research technicians. All differential leukocyte counts were done by the authors using supravital techniques for accurate cytological studies of erythrocytes and leukocytes. Hematocrit determinations and blood volumes were not obtained because of the immaturity of the great majority of the patients studied.

The majority of the patients were given a preparation containing cobalt chloride 40 mg. (equivalent to 9.9 mg. elemental cobalt) and ferrous sulfate, 75 mg. per 0.6 cc. of an aqueous solution stabilized with citric acid. A few of the patients received a plain aqueous solution of cobalt chloride containing 40 mg. per 0.6 cc. Dosage with either preparation was 0.6 cc. administered orally three times daily immediately after meals. These preparations proved acceptable to all our patients and were well tolerated. In the entire group only three showed any toxic reactions. These consisted of anorexia, mild nausea, and, rarely, vomiting. It was ascertained that reactions occurred in each of the three patients because medication was given before meals. Shift to *post cibum* medication quickly terminated such troublesome reactions.

NUTRITIONAL IRON DEFICIENCY ANEMIAS OF INFANCY

1. *Effect of cobalt-iron mixtures on erythrocytes:* It was found, as others have indicated, that when cobalt was given in relatively large amounts it

was a very effective stimulus to erythropoiesis (fig. 1). It was our experience that in these infants 120 mg. of cobalt chloride per day seemed to provide maximal hematopoietic stimulation without troublesome toxic reactions.

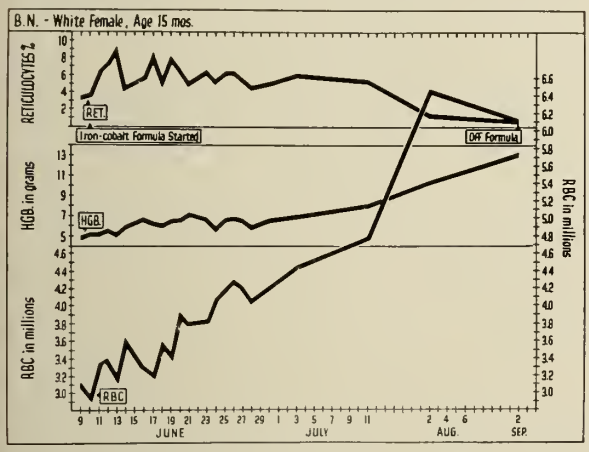

Fig. 1. Representation of cobalt-iron therapy effects upon red cells, hemoglobin and reticulocytes (case 13).

For maximal periods of erythrocyte increase this group of 23 patients showed an average gain of 100,100 erythrocytes per day. This average gain corresponds to that reported by Caussade and Petitdant[15] in a similar study of hypochromic anemias in infancy, and is almost threefold that anticipated[17] when iron alone is employed.

The degree of erythrocyte increase had no direct relationship to the level of circulating erythrocytes at the start of therapy.

Erythrocytes did not increase at an even pace in the majority of the patients studied. There was, instead, a series of primary, secondary, and even tertiary erythrocyte peaks and valleys. The primary peak occurred on the second to ninth day of therapy with the greatest number peaking on the second or third day after cobalt therapy had been initiated. Secondary peaks appeared from the fifth to the forty-sixth day with the majority peaking on the tenth to the fifteenth day. Tertiary peaks appeared from the eleventh to the twenty-third day with the majority peaking between the fifteenth and the twentieth day.

After 21 days the erythrocyte levels of most of our patients stabilized to a steady gain, or loss in those instances in which erythremic levels had previously been attained. In no instance did we observe sustained erythremic levels even though cobalt-iron therapy was maintained for periods up to one hundred days.

The erythrocytes continued to show characteristic anisocytosis, poikilocytosis, microcytosis, and achromia until hemoglobin levels of at least 12 gm. per 100 cc. of blood had been attained.

2. *Effect of cobalt-iron mixtures on reticulocytes:* Reticulocytosis showed greater variability than erythrocytosis. In this group of 23 patients the maximal reticulocyte peak averaged out at 6.9 days. The earliest maximal reticulocyte peak occurred on the second day of therapy, and the latest maximal reticulocyte peak occurred on the sixteenth day. Twelve of the 23 patients had maximal peaks in the first five days of therapy.

Primary peak reticulocytosis occurred in the majority of our patients between the second and fifth day of cobalt-iron therapy. Secondary and tertiary reticulocyte peaks, while they occurred, showed no predilection for any given period and were scattered widely between the fifth and twentieth days of therapy.

The highest reticulocyte peak observed was 23 per cent. The lowest was 3.4 per cent. Six patients had reticulocyte levels in excess of 10 per cent.

3. *Effect of cobalt-iron mixtures on hemoglobin synthesis:* Hemoglobin values showed a steady progressive increase over the period of study. This stood out in striking contrast to the erratic erythrocyte increment observed.

This group showed an average daily gain of 0.128 gm. of hemoglobin per 100 cc. of blood. Ten patients showed a daily hemoglobin gain of 0.15 gm. per day or better with the maximal gain of 0.28 gm. per day occuring in one patient.

Such hemoglobin gain is equal to that obtained by a good iron preparation alone, although most of such preparations contain larger doses of iron. Since the dosage employed contained 25 per cent less iron than the infant iron preparation recommended by Wintrobe[17] and 45 per cent less than the amount used by Kato,[7] this might be evidence for increased hemoglobin synthesis, as has been claimed by others.

4. *Effect of cobalt-iron mixtures on platelet levels:* Eleven patients demonstrated no significant alteration in circulating platelets while on cobalt-iron therapy. In the other twelve patients platelets were increased twofold or more while on treatment. In six of these patients platelet levels in excess of 3,000,000 per cu. mm. were observed. Two of these patients were particularly interesting. In one patient (case 12) the platelet level rapidly climbed to 7,000,000 per cu. mm. (fig. 2), and in the other patient (case 16) the platelets rose to a top level of 5,800,000 per cu. mm. (fig. 3). In both these patients cobalt therapy was stopped and elixir of ferrous sulfate alone was given. When cobalt was dis-

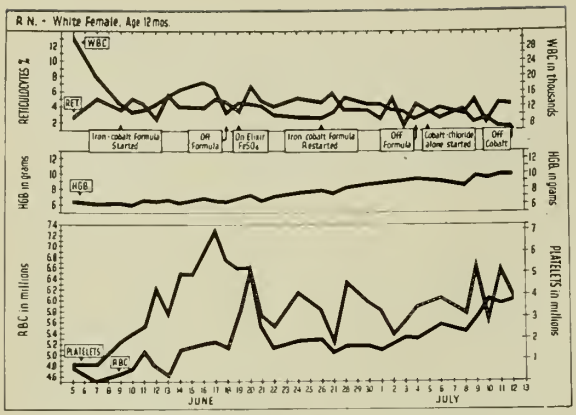

Fig. 2. Representation of platelet response to cobalt-iron therapy (case 12).

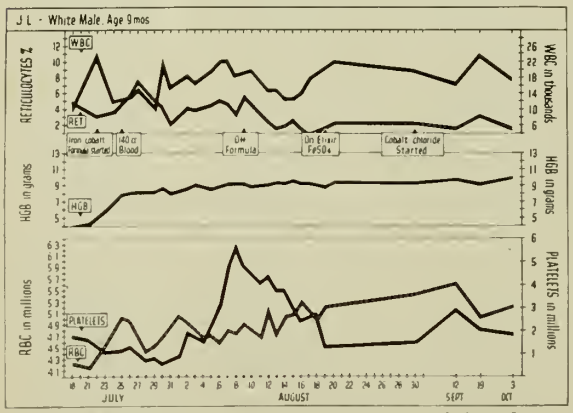

Fig. 3. Representation of platelet response to cobalt-iron therapy (case 16).

continued there was a prompt fall in platelets to high normal levels. Upon reinstitution of cobalt therapy, employing a plain aqueous solution of cobalt chloride alone, platelet levels of 3,800,000 and 3,000,000 per cu. mm. respectively were again rapidly reattained in each case. It would seem then, that the cobalt itself was directly responsible for the effect upon the platelet levels.

5. *Effect of cobalt-iron mixtures on circulating leukocytes:* The majority of the patients showed some alteration in leukocytes while receiving the medication. If a total leukocyte count of 12,000 per cu. mm. is accepted as the upper limit of normal, seven patients developed significant leukocytosis while receiving cobalt-iron therapy. All of these seven showed an increase of 5,000 leukocytes per cu. mm. or more. In one patient an increase of 13,550 leukocytes per cu. mm. was observed. In this patient values of 21,500 leukocytes per cu. mm. were obtained while on therapy.

There was no alteration in the relative values of polymorphonuclear neutrophilic leukocytes, lymphocytes, and monocytes with the exception of one patient (case 12) in whom there was an absolute gain of 5,830 polymorphonuclear neutrophilic leukocytes per cu. mm. of blood on the second day of cobalt-iron therapy.

In 16 of the 23 cases observed there was a significant increase in circulating polymorphonuclear eosinophilic leukocytes while on cobalt-iron therapy. In these patients eosinophils were increased above 6 per cent, or, in those patients who demonstrated eosinophilia before therapy was started, eosinophils were more than doubled. In three patients differential eosinophil counts of 34 per cent, 24 per cent and 22 per cent respectively were attained while on cobalt-iron therapy.

In 12 of the 23 studied patients a significant increase in circulating polymorphonuclear basophilic leukocytes was observed. In this group differential leukocyte counts revealed basophil counts in excess of 3 per cent or double the number when basophils exceeded 3 per cent before therapy was instituted. The three highest basophilic counts were respectively, 18 per cent, 12 per cent, and 6 per cent while on cobalt-iron therapy.

COBALT THERAPY IN HYPOPLASIA OF THE BONE MARROW

Because of the effect demonstrated upon all the circulating elements, we were much interested in employing cobalt in various hypoplasias of the marrow. Seaman[18] had previously noted a beneficial effect of cobalt in chronic erythrocytic hypoplasia without thrombocytopenia and granulocytopenia. Three patients came under our observation of whom two were adults (cases 24 and 25) and one was an infant (case 26). The adults were given 200 mg. of cobalt chloride per day orally. The infant was given 120 mg. of cobalt chloride per day. Case reports are appended and a brief discussion is given under each case.

Case 24. This 81 year old white male was admitted to the Indiana University Medical Center in July 1952 as a case of possible bowel obstruction with a history of recurrent episodes of upper abdominal pain and vomiting of one year's duration. Present episode had begun one week prior to admission. He had had no bowel movement for six days. Physical examination revealed an elderly white male in no acute distress. There was a slight serosanguineous discharge from the right ear. The chest was emphysematous. No rales were heard. Examination of the cardiovascular system revealed no abnormalities. B.P. was 130/70. Abdomen was relaxed and no definite tenderness could be made out. Liver, kidneys, and spleen were not palpable. Fecal matter could be palpated in the descending colon in the left lower quadrant. Rectal examination revealed a fecal

impaction. Prostate was normal. Laboratory findings: Urinalysis was normal. T.N.P.N. was 41 mg. per cent. Stools were negative for parasites. Gastric analysis with alcohol-histamine meal revealed complete absence of free hydrochloric acid. Hemogram on admission revealed: hemoglobin of 7.4 gm.; total erythrocyte count of 1.85 million per cu. mm; total white count of 3350 per cu. mm. with a differential leukocyte count of 44 per cent, polymorphonuclear neutrophils, 2 per cent basophils, 10 per cent eosinophils, 28 per cent lymphocytes, 16 per cent monocytes. The erythrocytes were macrocytic and there was marked anisocytosis and poikilocytosis. Total platelet count was 168,010 per cu. mm. Reticulocytes were 0.6 per cent. Bone marrow examination revealed marked hypocellularity with hypoplastic fragments largely replaced with fibrin and fat. There was a marked diminution in nucleated red cells with arrest at early and late erythroblast levels. There was an increase in plasma cells, phagocytic clasmatocytes, and tissue basophils. Megakaryocytes were diminished in number. There were no leukemic changes and no invading tumor cells seen. This markedly hypoplastic marrow showing toxic changes did not support a diagnosis of primary pernicious anemia which had been suggested by the peripheral blood picture. X-rays: Three barium enema x-rays including double contrast studies were negative. X-rays of upper gastrointestinal tract were also negative. Chest x-ray revealed fibrosis of left apex. Intravenous pyelogram was normal. Course in hospital: Diagnosis of subacute bone marrow hypoplasia of unknown etiology was made, after careful search had failed to reveal any evidence of neoplastic disease. The hemoglobin had been increased to 11.6 gm. and the erythrocyte count to 3.17 million per cu. mm. by two blood transfusions of 500 cc. each. Because of the low white and platelet counts it was felt that a trial of cobalt chloride therapy was indicated. On July 22, 1952 patient was placed on cobalt chloride, 200 mg. per day in three divided doses. Response to this therapy is shown graphically in figure 4. Repeat bone marrow examination on August 8, 1952 after 18 days of therapy revealed a large number of fragments. Compared with the previous examination before therapy there was a striking increase in the cellularity of both the fragments and diluent marrow. All marrow elements now appeared to be present in normal quantities. There was excellent erythropoiesis with some left shift of the nucleated red cells to early and late erythroblast levels, but no maturation arrest. No evidence of marrow toxicity could be found. Peripheral count on the same date revealed hemoglobin of 12.9 gm. Total erythrocyte count was 4.01 million per cu. mm. Total white count was 6150 per cu. mm. with differential showing 62 per cent polymorphonuclear neutrophils, 2 per cent basophils, 12 per cent eosinophils, 18 per cent lymphocytes, 6 per cent monocytes. Total platelet count was 773,931 per cu. mm. Reticulocytes were 1.2 per cent. Patient was discharged from the hospital on August 9, 1952. Unfortunately no follow-up studies on this patient were available.

This patient, while he had histamine-fast achlorhydria, demonstrated a hypocelluar marrow with no megaloblasts. His marrow showed widespread moderately severe toxic changes with considerable increase in plasma cells, phagocytic clasmatocytes, monocytes and lymphocytes. His marrow fragments consisted largely of fatty debris, fibroblasts, and phagocytic clasmatocytes with a scattering of tissue basophils. Eighteen days after institution of cobalt chloride therapy his circulating blood elements showed values as follows: red blood cells, 4,010,000; hemoglobin, 12.9

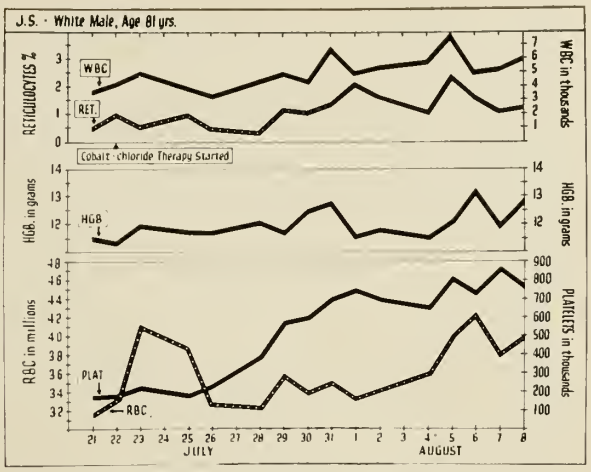

Fig. 4. Representation of peripheral blood response to cobalt chloride therapy in hypoplastic anemia (case 24).

grams; white blood cells, 6,150; platelets, 773,931; and reticulocytes, 1.2 per cent. These are contrasted with pre-treatment values of: red blood cells, 3,190,000 hemoglobin, 11.6 grams; white blood cells, 3,350; platelets, 168,010; and reticulocytes, 0.6 per cent (see fig. 4).

Eighteen days after institution of cobalt therapy his bone marrow was re-examined with a complete and gratifying change in the marrow picture. At this time granulocytopoiesis, erythropoiesis, and megakaryocytopoiesis were present in abundance and all evidence of toxic damage had disappeared. He failed to meet his outpatient clinic appointments so that follow-up studies are unfortunately not available.

Case 25. This 38 year old white female was admitted to the Indiana University Medical Center on July 18, 1952 because of a chronic anemia which had been present for six years and had been refractory to all therapeutic agents tried (iron, liver extract, vitamin K, vitamin B_{12}). During the past two and one-half years she had received a total of 57 whole blood transfusions. There was no history of exposure to any toxic substance or drug preceding the onset of her anemia. There had been no purpura or jaundice. The only history of blood loss was that of menorrhagia during recent years. Physical examination revealed a well developed and nourished, dark complexioned individual in no apparent distress. There were no skin lesions. Eyes, ears, nose and throat were normal. Chest was clear. Heart was not enlarged. There was a soft systolic murmur along the lower left sternal border. B.P. was 130/80. Liver edge descended 2 cm. below the right costal border on deep inspiration. Spleen was not palpable. No abdominal masses were made out. Pelvic and rectal examinations were negative. Laboratory findings: Urinalysis was normal. Serology was negative. Total serum bilirubin was 0.4 mg. per cent. Prothrombin time was 100 per cent of normal. T.N.P.N. was 29 mg. per cent. Gastric analysis revealed large amounts of free hydrochloric acid after histamine stimulation. Endometrial biopsy was not diagnostic. E.K.G. showed only multiple premature ventricular contractions. Chest x-ray was normal. Hemogram was as follows: Hemoglobin was 6.7 gm.; total erythrocyte count was 2.38 million per cu. mm.; total leukocyte count was 2900 per cu. mm. with differential showing 58 per cent polymorphonuclear neutrophils, 2 per cent neutrophilic "C" myelocytes, 24 per cent

lymphocytes, and 16 per cent monocytes. Total platelet count was 167,220 per cu. mm. Reticulocytes were 0.7 per cent. Sickling preparation was negative. Erythrocyte fragility was normal. Bone marrow revealed only a few small fragments and marrow was very hypocellular. Fragment consisted for the most part of fat, fibroblasts, occasional reticulum cells, and replacement lymphocytes with only a scattering of granulocytes. There was marked diminution in nucleated red cells and megakaryocytes. This was thought to represent a chronic moderately severe hypoplasia of all marrow elements. Course in hospital: Patient was given a trial of cobalt chloride therapy consisting of 200 mg. daily in three divided doses for a period of 17 days. At the end of this period there had been no discernible effect on the blood count which was as follows: Hemoglobin was 5.3 gm.; total erythrocyte count was 1.73 million per cu. mm.; total white count was 4050 per cu. mm. with differential of 56 per cent polymorphonuclear neutrophils, 28 per cent lymphocytes, and 16 per cent monocytes. Total platelet count was 161,620 per cu. mm. Reticulocytes were 0.8 per cent. After this failure to respond to cobalt chloride therapy, patient was transfused and discharged August 12, 1952 on folic acid and vitamin B_{12} therapy.

On admission to the hospital peripheral blood studies were obtained revealing the following values: red blood cells, 2,380,000; hemoglobin, 6.7 grams; white blood cells 2,900; platelets, 167,000; and reticulocytes, 0.7 per cent. Marrow fragments were sparse and on microscopic examination consisted only of fat, reticulum cells, and lymphocytes. The differential values, except for rare nucleated red blood cells did not differ significantly from those found in the peripheral blood. A diagnosis of advanced chronic marrow hypoplasia, cause undetermined, was entertained and oral cobalt chloride was started. After eighteen days of therapy there was no significant improvement in peripheral blood values, and she was considered a cobalt failure. Other therapeutic measures were employed and to date her condition has remained unchanged.

Case 26. This 23 month old white male infant was admitted to the James Whitcomb Riley Hospital for Children on September 13, 1952. His present illness had begun in June 1952, at which time he had had a sudden onset of chills and fever accompanied by convulsions. This initial illness was of only a few days duration responding to antibiotic and antipyretic medications. About three weeks later listlessness and pallor became prominent. Diagnosis of anemia was made by the family physician, and patient was given a blood transfusion. In August 1952 pallor again became prominent and patient began having intermittent fever, which at times reached a peak of 103° F. At this time he was given vitamin B_{12} and penicillin injections three times a week. Because of failure to respond to therapy he was admitted to another hospital where a bone marrow aspiration was said to have shown "hypoplasia of the marrow." Past history revealed that in August 1951 patient had accidentally ingested some insect repellant with no demonstrable ill effects. Sometime during the spring of 1952, child was found with a bottle of rat poison, but it was not known how much if any he had ingested. At least no toxic symptoms were noted at the time.

Physical examination on admission to the James Whitcomb Riley Hospital revealed an irritable child who appeared dehydrated and acutely ill. Temperature was 102° F. A papular erythematous rash was present over the extremities. Eyes, ears, nose and throat were normal. There was a brassy cough and fine crepitant rales in both lung bases. Cardiovascular system was normal. Liver was palpable 2 cm. below the right costal margin. There was no splenomegaly. Laboratory findings: Urinalysis was essentially negative. Total bilirubin was 1.2 mg. per cent with an indirect of 0.95 mg. per cent and a 1 minute value of 0.25 mg. per cent. Heterophile agglutinations were negative. Complement fixation test for histoplasmosis was negative. Stools were negative for parasites. Blood cultures were repeatedly negative. Nose and throat cultures revealed no significant organisms. Skin biopsy was not diagnostic. Hemogram on admission was as follows: Hemoglobin was 10.3 gm.; total erythrocyte count was 3.39 million cu. mm.; total white count was 1250 per cu. mm. with a differential of 4 per cent polymorphonuclear neutrophils, 80 per cent small lymphocytes, 4 per cent intermediate lymphocytes, 4 per cent young monocytes and 8 per cent monoblasts. Total platelet count was 10,170 per cu. mm. Reticulocytes were 0.1 per cent. Two bone marrow aspirations from the ilium and manubrium respectively both showed extreme hypocellularity and no demonstrable fragments. Only a rare nucleated red blood cell was seen and granulocytosis was sharply inhibited. There was an increase in irritation type lymphocytes, plasma cells, young monocytes, and atypical monoblasts. This marrow hypoplasia was confirmed by surgical biopsy of the bone marrow.

Course in hospital: X-ray films of the chest at the time of admission showed nodular infiltrations throughout both lung fields extending out from the lung roots. Because of these pulmonary lesions, the patient was placed on penicillin therapy; streptomycin therapy was later added because there was no clinical response on penicillin alone. Cobalt chloride therapy was instituted on September 20, 1952 with a dosage schedule of 120 mg. daily in three divided doses. On cobalt therapy, platelets returned to normal levels in nine days and the white count rose rapidly with leukocytosis developing in three days. Peak reticulocytosis of 20.3 per cent occurred on October 7, 1952. This hematological response is shown graphically in figure 5. A repeat bone marrow examination on September 30, 1952, revealed a great number of tiny fragments and excellent cellularity in sharp contrast to previous bone marrow examinations. Neutrophilic granulocytic and megakaryocytic activity were most pronounced, but there was good erythropoiesis, with no evidence of maturation arrest. Bone marrow cultures to date have been negative. During the first week of hospitalization pulmonary lesions increased, becoming diffuse, fluffy infiltrates and temperature remained high. Since then the pulmonary lesions have remained stable, and fever has been reduced. At the date of this writing the patient is still receiving antibiotic and cobalt chloride therapy. The exact diagnosis of the pulmonary lesions has not yet been established. The last hemogram on October 9, 1952 showed: hemoglobin 10.5 gm. Total erythrocyte count was 3.64 million per cu. mm. Total white count was 7950 per cu. mm. with differential of 46 per cent polymorphonuclear neutrophils, 1 per cent basophils, 1 per cent eosinophils, 35 per cent small lymphocytes, 1 per cent intermediate lymphocytes, 12 per cent mature monocytes, and 4 per cent young monocytes.

On admission to this hospital this boy revealed marked hepatomegaly, a scattered papular dermatitis, and diffuse

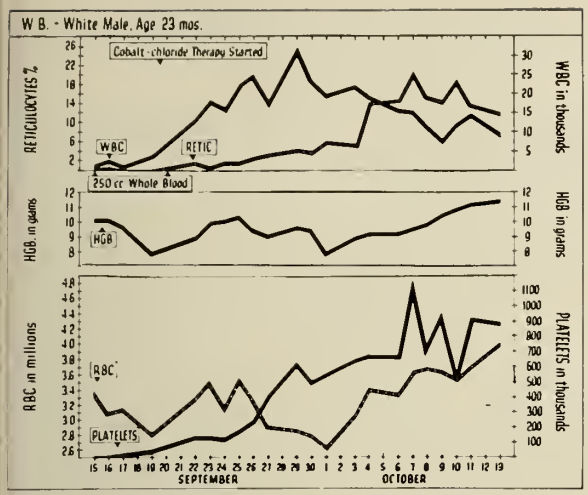

Fig. 5. Representation of peripheral blood response to cobalt chloride therapy in hypoplastic anemia (case 26).

bilateral pulmonary infiltrates. His peripheral blood revealed the following values: red blood cells, 3,390,000; hemoglobin, 10.3 grams, white blood cells, 1250; platelts, 10,170; and reticulocyte, 0.1 per cent. He had been subjected to two previous bone marrow aspirations at Ball Memorial Hospital in Muncie, Indiana, and the pathology group there had made a diagnosis of severe marrow hypoplasia. Two bone marrow aspirations by us failed to yield marrow fragments and the only cellular constituents we observed were sparse, scattered immature, monocytes, monoblasts, irritation lymphocytes and atypical occasionally multi-nucleated plasma cells. Only rare, very immature myelocytes and early erythroblasts were observed. A diagnosis of advanced subacute hypoplasia of the marrow was entertained and this was confirmed by surgical biopsy of the marrow. Oral cobalt chloride therapy in a dose of 120 mg. per day was instituted. Two days after institution of therapy the peripheral blood revealed the following values: red blood cells, 3,300,000; hemoglobin, 9.0 grams; white blood cells, 13,550; platelets, 145, 200 and reticulocytes, 1.3 per cent. Inspection of figure 5 demonstrates the continuing hematological response. A bone marrow aspiration obtained 10 days after institution of cobalt therapy revealed a complete reversal of the previous five bone marrow examinations with re-establishment of a normal marrow picture.

While it is, of course, possible that institution of therapy was coincidental with a spontaneous remission of his severe marrow hypoplasia, the speed with which this remission occurred and the gratifying sharp response in all values would suggest that the cobalt was of supplementary, if not of primary benefit.

COMMENT

These studies suggest that cobalt has a profound effect, not only upon erythroid elements but in some instances, at least, upon platelets and white blood cells as well.

No direct evidence as to how cobalt therapy elevates all peripheral blood elements was found but several inferences seem to be suggested by the accumulated data.

Like Weissbecker[14] it is felt that cobalt, initially at least, causes rapid mobilization of reservoir cellular elements. In the previous data on erythrocyte and reticulocyte peaks it should be noted that there was a rapid mobilization of erythrocytes which appeared almost simultaneously with, or, in some instances, antedating initial reticulocyte peaks. This is certainly not the usual relationship in the erythropoietic cycle where erythrocytosis lags many days behind reticulocytosis. What cellular reservoirs contribute to this increment we have not determined.

The work of Davis and associates[4] in duck anemia would suggest that cobalt may interfere with erythrophagocytosis. This view point is indirectly supported by Wolff[10] who found cobalt to be of benefit in patients with hemolytic anemias. On the basis of our data we can neither confirm nor deny this postulate.

The data would certainly suggest that on prolonged therapy, cobalt is a very potent stimulus to erythropoiesis, leukopoiesis, and megakaryocytopoiesis. This is strongly suggested by the response of two of our patients with marrow hypoplasia. These two patients had demonstrated rather prolonged severe depression of all circulating elements. While rapid, spontaneous remissions are not remarkable in simple agranulocytosis, such is not the usual anticipated course of events in so-called "aplastic anemia," which these two patients seem to represent. Cobalt appeared to be of at least supplementary value in obtaining their prompt, gratifying hematological recovery.

The hematological findings in these patients resemble the picture observed in polycythemia rubra vera with erythremia, leukocytosis, and thrombocytosis. The eosinophilia and basophilia which occurred in many patients augment such a resemblance. In contradistinction to polycythemia rubra vera, however, the patients had as much increase in lymphocytes as they did in neutrophilic granulocytes. Whether the age of these patients conditioned the lymphocyte response cannot, at this time, be determined. Further clarification of cobalt effect on hemoglobin synthesis is in progress.

When using cobalt chloride therapeutically dosages less than 120 mg. per day in children and 200 mg. per day in adults will not yield maximal results. When dosages do not exceed these values and are not given before meals toxic reactions should not be encountered.

These studies demonstrate a theoretical hazard in the therapeutic use of larger cobalt dosages. While platelet levels of 3,000,000 to

7,000,000 per cu. mm. were tolerated with impunity by these infants, such might not prove to be the case in adults or in those with vascular disease or trauma. In such patients some attention should be given to serial determinations of circulating thrombocyte levels.

Cobalt-iron preparations would probably be most effective in those instances where iron deficiency is associated with some inhibition of erythropoiesis. This has been noted by other authors in treating the anemias associated with chronic infectious processes and malignancies.

Some provocative observations were obtained in two patients with hypoplasia of the marrow and further investigations evaluating this data are contemplated. While little absolute information can be derived from such brief data it is believed that cobalt, to be effective, should be used while marrow damage is acute or subacute. Little can be anticipated in those individuals whose marrow has become devoid of potential hematopoietic foci.

SUMMARY

A cobalt-iron preparation containing 70 mg. of ferrous sulfate and 40 mg. of cobalt chloride for each 0.6 cc. of aqueous solution was used in the treatment of 23 infants with uncomplicated nutritional iron deficiency anemias.

In two adults and one infant with moderately severe to severe pan-marrow hypoplasia, cobalt chloride alone was administered in 120 to 200 mg. dosage per day.

The preparations were acceptable and tolerated without appreciable toxic reactions.

Cobalt caused markedly increased levels of circulating erythrocytes, leukocytes, and thrombocytes in the majority of the patients, and in some there was noted a significant elevation of circulating eosinophilic and basophilic leukocytes.

Some possible mechanisms by which these elevated levels could be obtained with cobalt were discussed.

Possible indications for cobalt and cobalt-iron preparations were also suggested.

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It is an intangible thing – this distinctive character of one hospital which makes it differ from others of its kind. Like an old wine, it has acquired a certain quality which comes only with age, and which a new institution cannot imitate, for it represents the fusion of the countless personalities of all those who have worked for it or in it, no matter how empty, no less than that of a trustee or superintendent or member of the staff.

Harvey Cushing: *The Personality of a Hospital*

The Rorschach Test and Its Forensic Implications

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When a medical witness qualifies himself as an expert in a given field he exposes himself to cross-examination which is sometimes ruthless. One of the several techniques of cross-examination employed by the opposition in civil, criminal and industrial cases is to emphasize the difference between "subjective" and "objective" symptoms. Especially during a jury case the opposition will play up the "subjective" aspects of the question and will sometimes manage to get across to the jury the impression that the plaintiff, petitioner or defendant has ulterior motives. Elsewhere[1] I have discussed the difference between traumatic neurosis, compensation neurosis, and the relatively new concept of attitudinal pathosis.

When a qualified medical expert can bring into court x-ray films, laboratory records and historical facts, he is well fortified. But, all too frequently, the psychiatric expert witness must leave himself open for a cross-examination onslaught stressing the patient's "subjective" symptoms upon which he is basing his opinion. Therefore, if he can show something in the nature of "objective" findings his opinion is reinforced.

The Rorschach test is one of a number of techniques by means of which one can obtain objective evidence of an individual's personality configuration. Just as a roentgenogram gives a three dimensional view of the physical structure of the body, so does a psychogram (Rorschach analysis) give a three dimensional view of the psychic structure of the personality. It is a projective technique using the recording, scoring and interpretation of the subject's responses to 10 standard ink blots. Inasmuch as each blot is in itself meaningless, it constitutes an amorphous stimulus and what the subject tells the examiner is a reflection of the patient's own personality. The following case report demonstrates the forensic value of the Rorschach.

In May 1925, X, a 22 year old married male licensed to practice law in the State of Minnesota, obtained employment as an attorney in a county agency. He was said to have had a good record as far as his professional ability and his personal habits were concerned. For the next 13 years his record was good. However, on December 5, 1938 he pled guilty to the crime of indecent assault. The history of his offense was as follows.

On November 28, 1938, a 15 year old boy made a statement to the police that in July, X had invited him to his (X's) home under pretext of giving him a job. When the boy arrived at the house, X asked him upstairs, took off his own clothes, had the boy do likewise, and then performed fellatio on him. Following the act X gave the boy a dollar and told him not to mention anything about it to his parents or there would be trouble. During the next four months this happened about seven times, and on the last two or three occasions X induced the boy to perform fellatio on him. According to the boy's statement, he "didn't seem to like it." Eventually, through a combination of circumstances which need not be described here, the boy's parents discovered the affair and on November 30, 1938, X admitted the whole story to the police and corroborated the boy's account of the details as to time and place. However, as is the custom with sexual psychopaths, X offered a number of extenuating circumstances.

The offender was sentenced to a penal institution where he remained for 18 months. During this time his wife obtained a divorce and X also was disbarred from the practice of law. He was paroled from the penitentiary early in May 1940.

On June 1, 1940, X was arrested upon complaint of three boys who claimed that he had approached and made improper suggestions to them while they were eating in a hamburger restaurant. When he arrived at the police station X gave the usual story about having been joking, not intending anything serious or suggestive and of having spoken "all in fun." He was about to be released from custody when one of the officers asked him if he ever had been in trouble before. Thereupon he revealed that he had served time because of a sex offense and was now on parole. Contact was made with the parole officer and arrangements were made to return X to the penitentiary. In the meantime X's mother who believed that her son could do no wrong became active and filed a petition asking that he be examined by the Probate Court to determine whether he was a psychopathic personality under the Minnesota law. He was so found and committed to the

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[1]Traumatic neurosis, compensation neurosis or attitudinal pathosis. A.M.A. Archives of N. and P.: 65:593-603, 1951.

state hospital at St. Peter, Minnesota for treatment. The record shows that while he was at St. Peter, X was accused by another inmate of having made "improper advances," but because the other inmate was himself a psychopath, it never was determined whether his allegations were true.

On January 5, 1942, X was discharged from the hospital at St. Peter with certain restrictive recommendations by the superintendent. Shortly after his release he married a woman of doubtful background. Although this second wife was obviously a psychopath and although she had at least one psychotic breakdown, X contended later that all was serene, that he was happily married, that his sexual adjustment with his wife was eminently satisfactory, and that he had gotten over his perverse tendencies.

Some time in 1944 X petitioned the Supreme Court of Minnesota for reinstatement to law practice, saying that he was happy, stable and had been rehabilitated. His petition was denied. In May of 1947, he again applied through counsel for reinstatement and offered written opinions from three reputable psychiatrists to the effect that he had recovered from his psychopathy and should be reinstated. There were also character references from a number of reputable attorneys who knew him and who said that he was morally and professionally fit to resume the practice of law. His own attorney sincerely believed that X had been the victim of "witch hunting" and that the committee that had denied his application in 1944 had been influenced by an account in a weekly magazine of the Army's report on homosexuality.

In view of the opinions expressed in the reports of the three psychiatrists who had examined X, the Practice of Law Committee of the Bar Association felt it advisable to produce some evidence of the same character, if possible, in opposition to the petition and to secure the opinions of their own expert, and to make the question of the respondent's complete recovery a question of fact. I was retained for this purpose.

After hearing a brief oral resume of the facts and questions involved I consented to examine the petitioner on July 6, 1947. I stated that I preferred not to see the reports of the other three psychiatrists and that I wanted to make my own examination, my own objective findings, and arrive at my conclusions independently.

Throughout the psychiatric interview X was very pleasant and cooperative. He gave every evidence of sincerity and of trying to give me all of the necessary facts. From his conversation and from his demeanor during the three hours he was in my consulting room one would say that X had solved his problem and that he was a well adjusted person. This impression corroborated the opinions of the three other psychiatrists. However, considering that this man was an attorney who knew more of the right answers than an ordinary layman, and recognizing the glib and facile ways in which a psychopath can present his side of a question, I decided that a vis-a-vis interview could not bring out the entire picture and that more subtle methods of exploring the subject's personality would be necessary. I was already skeptical about the value of a Pentothal or Amytal interview, and since then the evidential value of these techniques has been seriously questioned and, by some, denied. Therefore, it was decided to use the MMPI and the Rorschach.

On the MMPI, X answered all of the questions to the best of his ability, that is, he did not attempt to falsify any significant number of his answers. Moreover, there were no significant deviations in any of the categories covered by the test. There was a very slight elevation (T_{73}) in the score of "psychopathic deviate" but this is not conclusive.

On the other hand, the Rorschach showed that X was suffering from a deep character neurosis. I discussed the Rorschach protocol with Dr. Samuel J. Beck in Chicago to whom I am deeply grateful for his many hours of individual training in the Rorschach method. We concluded that while X's adaptive mechanism functioned smoothly at times, there was evidence that he would frequently "split off" a response having bizarre content and extremely unusual association. He showed compulsivity, autism, and considerable unhealthy fantasy which was functioning in a personality whose ego control was not strong enough to bind it. There was deep, pervasive central anxiety and definite evidence of neurotic shock. Associational content showed responses that are commonly given by homosexuals. My conclusion was that X's antisocial behavior was symptomatic of his character neurosis, that evidences of the character neurosis persisted, and, while at the behavioral level X seemed to have stabilized and to be sincere in his efforts to remain stabilized, he would relapse under stress. His chances for avoiding relapse were relatively poor, while his chances for relapsing were preponderate (see table I).

TABLE I

The psychogram was as follows:

R = 60

W	4	M	9	(−, 2)	H	5	F+	70%
D	37	CF	1		Hd	9	A	25%
Dd	19	FC	1		A	11	P	7
	60	Y	2		Ad	4	S	10
		FY	1		An	3		
		FVY	1		Cg	4		
		FV	1		Ge	3		
		F	7		HH	3		
		F−	11		Bt	3		
		F+	26		Misc	3		
			60		Ay	2		
					Imp.	2		
		EB 9/1.5			Pr	2		
					Rc	2		
Z = 48.0					Fi	1		
					Ls	1		
App: (W) D Dd!!					Mu	1		
					Na	1		
Seq: Meth- Irr.						60		

The F minus responses were wide deviations and bizarre. Many of the movement responses were flexor, were seen in Hd and in S, and expressed phantasies such as "lower part of a man with his arms folded or bent as if he were holding something" (head detail in V with card V), "a man kneeling and praying asking his Lord for help" (the lateral margin in VI with card <), "girls in half-stooped position peering around a corner away from me" (upper and middle details in VII with card V) and others. Many human figures were seen as men wearing women's clothes, masked with dominos, zippers or swimming trunks," etc. A complete interpretation would be too space consuming to be recorded here.

My report prompted an intensive investigation on the part of the Bar Association into X's activities and it was discovered that during his standard psychiatric interviews with his own experts and with me he had made numerous false statements concerning his past behavior, his marital status, his employment record, and that he had neglected to say anything about wide mood swings, alcoholic debauches and various homosexual episodes with young boys subsequent to his first petition for reinstatement in 1944. Accordingly his petition for reinstatement in 1947 was denied by the Supreme Court of Minnesota. We have no record of his subsequent activities.

In medico-legal cases there is another area in which the Rorschach test is helpful in arriving at an opinion concerning the mental status of an individual. That is in cases involving the post-accident syndrome. The question of whether a person who has been in a compensable accident is suffering from an organic syndrome, a neurosis, or whether he is malingering is many times a diagnostic enigma. We all know how the factor of monetary reimbursement for the injury, and the never-ending determination of legal responsibility can confuse a diagnosis. A patient may sustain the most severe skull trauma and not have sequellae; or, on the other hand, the slightest injury may result in symptomatology which may incapacitate the patient. Incapacitation may include everything from frank psychosis to mild anxiety states with excessive somatic preoccupation, usually involving the part of the body that was injured. Therefore, some test which would add to the neuropsychiatric armamentarium would be welcomed by physicians, the judiciary, workman's compensation commission, insurance companies, and the legal profession at large.

It is possible by the Rorschach method to differentiate between the organic syndrome, functional neuroses, and malingering. Space will not permit a detailed discussion of the Rorschach findings in these various categories but, suffice to say, they have been statistically validated and are considered reliable.

One of the criticisms of the Rorschach is that it is a complicated test, it is time consuming, and the findings of different workers are mutually inconsistent and contradictory. I concede that the test is complicated and time consuming, but these facts do not invalidate the test. As far as inconsistencies and inaccuracies are concerned, I believe that most of them can be attributed to improper training and lack of experience on the part of the person administering the test.

To make the Rorschach as objective as possible I suggest that the protocol on a given patient be scored and interpreted by two trained and experienced examiners. One interpretation should be made by the person who administered the test, and the other interpretation should be made "blind" from the protocol by another expert who has never seen the patient and who is unfamiliar with his history. Then the two interpretations should be compared and points of agreement as well as points of difference considered in the final analysis. In this manner, and perhaps through the use of other projective techniques (T.A.T., Szondi, etc.) a large part of the "subjective" vs. "objective" argument in forensic psychiatry might be resolved.

How much the practicing doctor cares about his patients as individuals apart from their being the source of his livelihood; how much the medical scientist may be interested in promoting science rather than in securing his own promotion; how much the teacher influences his pupils to their best efforts, unmindful of what the curriculum requires briefly of him; how much the student engages in his work for the work's sake, regardless of his marks and rating — all these things depend on a devotion which places spiritual above material regards.

Harvey Cushing: *Consecratio Medici*

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.*

Experimental Study of the Polarographic Cancer Test and of the Sulfhydryl Titration for the Differentiation Between Normal, Cancerous and Other Pathological Sera*

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IN 1936 Brdicka[1] introduced a polarographic method for the differentiation between normal and cancerous blood sera. This test was based on the observation that the catalytic waves obtained on electrolysis at the dropping mercury electrode of an ammoniacal cobaltic solution in the presence of alkali denatured and deproteinated cancerous sera generally are higher than those obtained with normal sera. The serum is denatured for a given time in dilute alkali hydroxide and the proteins removed with sulfosalicylic acid. The height of the catalytic wave in the filtrate was supposed to give an indication of the protcose content,[1] although recently the material responsible for the filtrate wave is believed to consist of mucopolysaccharides (see C. B. Huggins, Proceedings First Conference on Cancer Diagnostic Tests, 1950). Extensive studies have been carried out in various laboratories which showed that in about 80 to 90 per cent of cancerous sera the average wave height in the filtrate test is greater than in normal sera.[2] On the other hand among normal sera about 10 per cent give a positive cancer test. The test would be of considerable diagnostic value if it were not for the fact that a positive cancer test is obtained with sera of patients suffering from various diseases.[3,4] Quite generally a positive test is obtained with sera from people suffering from minor inflammations like common cold, bronchitis, etc. Table I summarizes in a comprehensive way the results reported in the literature on polarographic cancer tests.

In an effort to improve the original Brdicka test Müller and Davis[5,6] proposed the combination of two different polarographic tests carried out on the same blood sample. One of these tests is a modification of the Brdicka filtrate test with oxalated plasma. The other test gives the wave height obtained with whole alkali denatured (not deproteinated) plasma in an ammoniacal cobaltous buffer. The ratio of the wave heights obtained in the two tests ("protein index") is proposed as a method of representing the polarographic results. However, in our experience this modification does not make the test more specific for cancer.

Forssberg and Nordlander[7] suggested three polarographic tests which were combined to give a ratio which is high for normal and low for cancer sera. But also with this modification considerable overlapping between normal and pathological values is reported.

Recently the quantitative determination of sulfhydryl groups in blood sera by amperometric titration with silver nitrate has been found to be promising in the differentiation between normal and pathological sera.[8,9,10,11] Whereas several thousand results have been described in the literature on the Brdicka test little information is found on the reliability of the sulfhydryl determination for the detection of cancer. In the present paper a critical study has been made of the Brdicka method and a procedure is proposed which gives better reproducibility than the original Brdicka test. In many blood sera the results obtained with the modified Brdicka test in normal, cancerous and pathological noncancerous sera have been compared with the sulfhydryl con-

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TABLE I

RESULTS OF POLAROGRAPHIC CANCER TESTS REPORTED IN THE LITERATURE

Normal sera																
Number of sera tested	128[1]	45[2]	51[3]	67[4]												
Per cent positive*	11	9	0	9												
Cancerous sera																
Number of sera tested	35[1]	77[1]	37[1]	285[2]	176[2]	109[2]	97[3]	106[4]	59[5]	20[6]	500[7]	1,000[8]	85[9]	48[10]	24[12]	15,000[13]
Per cent positive*	71	83	80	90	93	89	99	74.5	90	100	96	85	72	92	8	
Per cent negative*								17.0					24			20
Per cent uncertain*								8.5					2			
Pathologic noncancerous sera																
Number of sera tested	28[1]	66[1]	237[1]	101[11]	20[4]											
Per cent positive*	50	65	67	49	55	(35 per cent negative, 10 per cent uncertain)										

* per cent positive (negative, uncertain) denotes per cent giving positive (negative, uncertain) cancer test.

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tents of whole sera. An attempt has been made to interrelate the results obtained in both tests. It is shown that the combination of both tests allows more definite conclusions than either test alone. Also, since the sulfhydryl determination is very simple and rapid it can be recommended as a routine procedure.

MATERIALS

Hexamine cobaltic trichloride obtained from Dr. H. A. Laitinen of the University of Illinois was recrystallized twice. The other chemicals used were commercial reagent grade products.

Stock solutions of 3×10^{-2} N cobaltic hexamine chloride were prepared. In agreement with Müller's[12] findings these solutions were found to be stable for several months. Stock solutions of ammonia were normal and five normal, and those of ammonium chloride and ammonium nitrate were normal. Potassium hydroxide solutions were normal and tenth normal. The concentration of the sulfosalicylic acid used was 20 per cent. The silver nitrate solution used for the titration of sulfhydryl groups was 10^{-3} M in $AgNO_3$.

EXPERIMENTAL

1. *The Brdicka Test*

Before the polarographic Brdicka test was applied for diagnostic purposes a detailed critical study of this test ("filtrate test") was carried out in order to find the best experimental conditions for reproducible results.

Preparation and storage of blood sera

Fresh blood was allowed to stand for about 30 minutes at room temperature and then centrifuged for 10 to 15 minutes. The supernatant serum was placed in a test tube and stored at 4° C. Brdicka[13] and Albers[3] mention that only fresh serum should be used in the test since old serum gives higher filtrate waves. We carried out Brdicka's test with sera which were allowed to stand at 4° C. for different periods of time up to ten days. We found an increase of about 30 per cent in the height of the filtrate waves after three to four days and a decrease upon further standing. After ten days the wave height was found to be smaller than that observed with fresh sera. Consequently, all the tests were made on the same day as the serum was taken from the patient.

Denaturation and deproteination; adsorption of proteose

Since the rate of alkali denaturation changes with temperature,[12] all our experiments were done at the same temperature ($25° \pm 0.1$). Denaturation was carried out with 0.05 N, 0.1 N, 0.2 N, 0.4 N, and 1 N, potassium hydroxide. Denaturation experiments with 0.1 N barium hydroxide gave practically the same results as those obtained with 0.1 N potassium hydroxide. This shows that the cation has no effect on the alkali denaturation of serum proteins as indicated by the polarographic proteose test. The best differentiation between normal and cancerous sera was obtained with 0.1 N potassium hydroxide. The time of denaturation was varied from zero to six hours. Denaturation time curves for normal and cancerous sera with potassium hydroxide of various concentrations are given in figure 1.

It is interesting to note that most of the normal sera tested gave a decrease in the height of the pro-

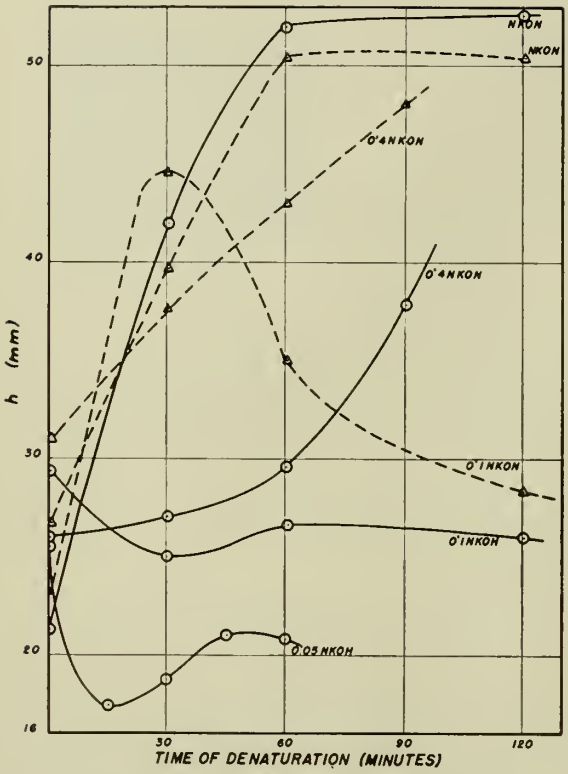

Fig. 1. Time of alkali denaturation vs. height of proteose wave (h) with SSA-centrifugates of normal and cancerous sera. Final dilution of serum 1:50, galvanometer sensitivity 1/5 m.m. ⊙——— Normal sera, △- - - - - Cancerous sera.

teose wave during the first 30 minutes of denaturation with 0.1 N potassium hydroxide. Then the wave height remained constant or increased again until after about one and a half hours no change was observed on further denaturation. Most of the pathological sera gave an increase in wave height within the first 30 minutes of alkali denaturation with 0.1 NKOH, followed by a decrease until after two hours the wave height was practically unchanged on prolonged denaturation (up to six hours). Since the wave height h_0 (at zero time denaturation) was found to be practically of the same magnitude for normal and pathological sera, it is evident that the best differentiation between normal and cancerous sera is obtained after 30 minutes of alkali denaturation with 0.1 NKOH at 25° C. In all our experiments we measured the wave heights h_0 and h_{30} after zero and 30 minutes denaturation respectively and also determined the ratio h_{30}/h_0. Generally this ratio tends to be smaller than one for normal and greater than one for cancerous sera. The analysis of the results indicated that the height of the proteose wave after 30 minutes of alkali denaturation is more significant than the ratio h_{30}/h_0. In the following tables and charts only h_{30} is therefore given for the proteose test of a serum.

After denaturation the sera were deproteinated by the addition of 20 per cent sulfosalicylic acid. The volume of sulfosalicylic acid added per 0.5 ml. serum was varied from 1.5 to 3 ml. and was found to have no effect on the height of the proteose wave. It was found by Brdicka[13] and confirmed by our experiments that the precipitated proteins must be removed as soon as possible from the supernatant liquid. Prolonged contact of liquid and precipitate leads to a decrease in height of the waves. According to Brdicka's procedure the liquid must be filtered ten minutes after precipitation. In our experiments it was noted that a clear filtrate was not always obtained by one filtration even when a hard filter paper (Whatman No. 5) was used. Refiltering resulted in a considerable decrease in wave height since proteoses are adsorbed by filter paper as previously reported by Winzler and Burk.[14] In order to obtain more reproducible results we used centrifugation instead of filtration. Centrifugates gave higher waves than filtrates obtained from the same serum. An Adams centrifuge with 3400 R.P.M. was used. Once the centrifugate is separated from the precipitate the proteose solution is fairly stable and no change in the proteose wave was observed when the electrolysis was made within eight hours after deproteination.

Some further experiments have been carried out on the adsorption of proteoses on adsorbents as in-

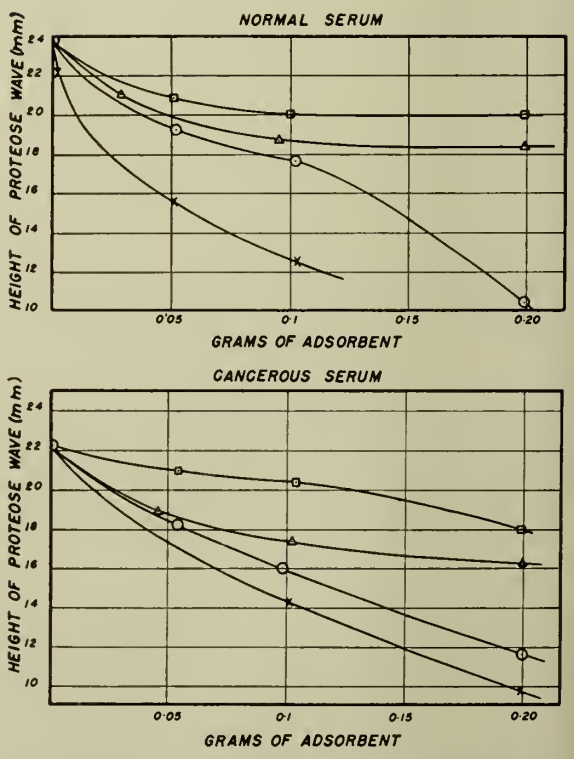

Fig. 2. Adsorption of proteose in SSA-centrifugates of a normal and cancerous serum on various solid. ⊡ Pyrexglass powder, △ Silicic acid, ⊙ Filter paper, × Alumina.

dicated by the decrease of the height of the catalytic waves. Three ml. of centrifugates obtained from normal and cancerous sera were shaken for five minutes with various amounts of the following four different adsorbents: shredded filter paper, ground pyrex glass wool, alumina treated with 0.1 N hydrochloric acid, and meta silicic acid. After centrifuging, the supernatant proteose solution was polarographed by the standard procedure. Figure 2 shows how the height of the proteose wave decreases on treatment with various amounts of adsorbents. Qualitatively the adsorption effect is similar for a normal and a cancerous serum. It appears that under the experimental conditions the adsorbing power of glass powder and silica for the polarographically active substances reaches a limiting value (about 0.1 g. per 3 ml. centrifugate of dilution 1:10). For filter paper and alumina the amount of proteose adsorbed increases more regularly with the amount of adsorbent added, and no limiting value was found with these adsorbents.

ELECTROLYSIS

The polarographic electrolysis was carried out at 25° C. ± 0.1° with one to two ml. of electrolyte in a test tube of about 7 cm. in length and 12 mm. diameter. A mercury pool of about 1 ml. was used as anode. All tests were done with the same capillary. The characteristics of the capillary used were: $m = 1.90$ mg. sec.$^{-1}$, $t = 3.3$ sec. at −1.5 volt vs. S.C.E., $m^{2/3} t^{2/3} = 3.41$ mg.$^{2/3}$. A Heyrovsky self-recording polarograph was used. The polarograms were taken over a potential range from −0.8 to −1.9 volt.

Most of our experiments with deproteinated sera were done with electrolyte solutions in which the dilution of the serum was 1:50 – that is, the amount of centrifugate contained in 5 ml. of electrolyte was obtained from 0.1 ml. serum. This solution was found to be convenient for the centrifugate test: (1) because it is within a concentration range in which the height of the protein waves is roughly proportional to the concentration of polarographically active substance in the electrolyte, and (2) because the amount of proteose present in the mixture in most cases is sufficient to eliminate the cobalt maximum. In those instances in which the proteose concentration was too small to suppress the cobalt maximum 0.02 per cent caffein was used as a maximum suppressor.[14] At this concentration caffein was found to have no suppressing effect on the catalytic proteose waves. This is at variance with Müller's findings[5] that caffein suppresses the proteose waves while it does not eliminate the cobalt maximum. In this connection it is interesting to note that the cobalt maximum in an ammoniacal cobaltic buffer which was 5×10^{-8} M in pepsin digested albumin could be eliminated by 0.02 per cent caffein only when the electrolyte contained some sulfosalicylic acid (1 per cent). In the absence of sulfosalicylic acid caffein had little effect on the cobalt maximum in the above experiment. The elimination of the cobalt maximum is important since it makes possible the accurate measurement of the diffusion current of the cobaltous wave ($Co^{++} \rightarrow Co$) which conveniently can be used as the base line for the measurement of the height of the catalytic waves. In all our experiments the height of the second peak (at −1.5 volt) of the proteose double wave is given as the characteristic value of h_{30}. The final solution in the electrolysis experiments was 3×10^{-3} N in cobaltic hexamine, 0.1 N in ammonium chloride and N in ammonia.

EXPRESSION OF THE RESULTS

In the following tables and figures the heights of the proteose waves are given in millimeters at a galvanometer sensitivity of 1/300. At this sensitivity 10 mm. on the current scale correspond to a current of 7.5 μA.

In agreement with Müller's[5] results we found that the height of the proteose waves is independent of the height of the mercury column. Müller determined the ratio between the height of the catalytic double wave and the product $m^{2/3} t^{2/3}$ (m being the mass of mercury per second and t the drop time in seconds) and found that this ratio is approximately constant for different capillaries. Thus, in order to compare catalytic waves obtained with different electrodes, the average values of the heights of the protein waves are also expressed by the ratio: current (in μA)/$m^{2/3} t^{2/3}$, as suggested by Müller.

2. *Amperometric titration of the sulfhydryl content in blood sera.*

Amperometric argentometric titrations at the rotating platinum wire electrode as indicator electrode were carried out in a way similar to that given for cysteine in aqueous medium.[15] The addition of alcohol to the titration mixture as suggested by Benesch and co-workers[8,9] may cause denaturation of the proteins and therefore was omitted in our titrations. The endpoint determined in aqueous medium was found to be sufficiently sharp. A systematic study of the argentometric amperometric RSH titration of glutathione and proteins in aqueous and nonaqueous media is now being carried out in this laboratory. The apparatus used for the amperometric titrations was similar to that described by Kolthoff and Harris.[16] A 1-ml. microburet divided into hundredths of a ml. was used in all titrations.

The titration results are expressed as mg. cysteine per 100 ml. serum.

RECOMMENDED PROCEDURES

Modified Brdicka Test

Denaturation, and deproteination

Into a dry 5 ml. volumetric flask place 0.5 ml. fresh serum. Add 1.25 ml. of 0.1 N potassium hydroxide. Shake well and allow to stand at 25° C. for 30 minutes. Then add 1.5 ml. of 20 per cent sulfosalicylic acid, shake, fill up to the mark with distilled water, shake again, transfer the contents into a 5 ml. centrifuging tube and centrifuge for about 8 minutes. Pour the clear centrifugate into a small stoppered flask.

Preparation for electrolysis

Place 0.5 ml. of a 3.10^{-2} N hexamine cobaltic solution into a 5 ml. volumetric flask. Add 0.5 ml. N NH_4Cl–, 1 ml. 5N NH_3– solution, about 1 ml. distilled water, 1 ml. of centrifugate, and fill up to the mark with distilled water. After shaking, transfer 1 to 2 ml. of the mixture into a dry electrolysis vessel, provided with a mercury pool anode. Introduce the dropping mercury electrode and electrolyze immediately at 25° C. Record the polarogram between −0.8 and −1.9 volt and measure the height of the peak of the catalytic wave h_{30} at about −1.5 volt, using the plateau of the cobalt wave at −1.2 volt as baseline. The final dilution of the serum in the electrolyte is 1:50. If a greater dilution in serum is required add 0.05 ml. of saturated caffein solution per 5 ml. electrolyte to suppress the cobalt maximum.

Amperometric titration of sulfhydryl groups

In a 150 ml. beaker provided with rubber stopper with holes for electrode, buret, salt bridge, and inlet tube for nitrogen, place 25 ml. of a solution which is 0.1 to 0.2 M in ammonia and 0.2 to 0.3 M in ammonium nitrate. Make the solution air free with nitrogen which is passed through during the entire titration. Add 0.5 ml. serum. Immerse the salt bridge, the rotating platinum wire electrode, and the tip of the buret in the solution and titrate with 0.001 N silver nitrate at an applied potential of −0.3 V vs. S.C.E. Plot the titration lines, the point of intersection corresponding to the end point.

RESULTS

The results obtained with the polarographic and amperometric tests are given in the following tables and in figure 3.

The "normal" sera were obtained partly from workers in the University of Minnesota hospital and in the School of Chemistry (together 17 samples) and partly from the Cancer Detection Center from 38 individuals over 45 years who had not been under previous health control. The data with the normal sera are not tabulated but given graphically in figure 3. Test results with sera from 42 individuals with various noncancerous diseases such as tuberculosis, benign tumors, cold, etc., are listed in table II. Table III gives the results obtained with sera from 91 persons with definite cancer diagnosis and from 5 persons with clinically questionable cancer. Tables II and III give the results of the centrifugate test (h_{30}) and amperometric test (RSH). The ratio of the two values h_{30} RSH is also given in tables II and III. The sera are specified by the clinical diagnosis whenever this information was available. Results obtained with cancerous sera for which the clinical diagnosis could not be secured are given in a summarized form in table III. The average values of h_{30}, RSH, and of the ratio h_{30}/RSH obtained with normal, pathological noncancerous and cancerous sera are listed in table IV. The average h_{30} in this table is given in both mm. and μA and also as the ratio h_{30} in μA / $m^{2/3}$ $t^{2/3}$.(5)

TABLE II

VALUES OF h_{30}, RSH, AND h_{30}/RSH IN NONCANCEROUS PATHOLOGIC SERA

Clinical Diagnosis	h_{30} *mm.*	*RSH mg. cysteine per 100 cc. serum*	h_{30}/*RSH*
1. Gangrene of foot	52.3	2.9	18.1
2. Gangrene of foot	12.3	6.4	1.92
3. Gangrene of foot	58.8	3.3	17.8
4. Gangrene from frostbite	40.5	4.2	9.64
5. Gangrene from frostbite	42.8	3.8	11.3
6. Diabetes	38.5	3.2	12.0
7. Hernia repair	49.2	3.6	13.7
8. Cystitis	53.5	3.9	13.7
9. Renal stones	26.0	5.7	4.56
10. Renal stones	22.5	5.5	4.10
11. Pyloric obstruction	41.5	5.3	7.83
12. Pancreatic cyst	48.0	2.9	16.6
13. Fistula in ano	51.5	4.2	12.3
14. Cholecystitis	26.5	5.1	5.2
15. Hemorrhoids	32.7	6.3	5.19
16. Ulcer on face	28.5	5.6	5.08
17. Tuberculosis	36.0	4.7	7.66
18. Fractured spine	50.5	4.7	10.8
19. Fractured cranium	40.5	4.4	9.2
20. Hyperparathyroidism	36.2	4.5	8.1
21. Mastectomy, cystic mastitis	38.8	5.0	7.8
22. Thrombophlebitis	50.2	3.4	14.8
23. Pyelonephritis and diabetes	36.0	3.9	9.2
24. Epilepsy, no brain tumor	33.5	5.3	6.3
25. Chromophobe adenoma of pituitary (H)	15.0	5.8	2.6
26. Lipoma (H)	15.5	4.8	3.2
27. Hyperthyroidism (H)	23.8	6.5	3.7
28. Plastic surgery of face	41.0	5.1	8.0
29. Cholecystectomy for cholecystitis	26.0	3.6	7.2
30. Parotid tumor	31.8	5.3	6.0
31. Tuberculoma (H)	20.0	3.3	6.1
32. Operation, no malignancy	25.2	6.1	4.1
33. Suspected cancer, none found upon operation	12.0	not done	—
34. Formerly had cancer, x-ray treatment, now benign ulcer on face	8.8	5.7	1.6
35. Formerly had cancer, none found upon operation	36.5	4.7	7.8
36. Toothache	34.0	not done	—
37. Cold, no fever	39.7	not done	—
38. Cold, no fever	35.8	7.0	5.12
39. Cold, no fever	34.5	5.9	5.85
40. Bronchitis, fever	50.0	5.0	10.0
41. Bronchitis, fever	48.6	5.2	9.35
42. Cold, no fever	31.5	5.8	5.43

(H) histologic

DISCUSSION

From table IV it is seen that in agreement with the literature the lowest average h_{30} is obtained with normal sera (20.2 mm.) while the highest value is that in cancerous sera (38.2 mm.); this average is 89 per cent higher than that in normal sera. The difference in the average RHS content between normal and cancerous sera is 42 per cent while the difference in the average ratio h_{30}/RHS between normal and cancerous sera is 355 per cent. It thus appears that the combination of the two tests may give more characteristic data than either test alone. It is interesting to note that the average h_{30} for noncancerous but pathological sera (36.8) is fairly close to the cancer value (38.2) while the average RSH value of noncancerous pathological sera (5.1) is closer to the normal average RSH (6.6). Although the number of sera investigated is not sufficient to

TABLE III

VALUES OF h_{30}, RSH, AND h_{30}/RSH FOR CANCEROUS SERA

Clinical Diagnosis	h_{30} (mm.)	RSH°	h_{30}/RSH
1. Adenocarcinoma of stomach (H)	53.5	4.5	11.9
2. Squamous carcinoma of floor of mouth	28.5	4.2	6.8
3. Squamous carcinoma of floor of mouth (H)	32.0	5.1	6.3
4. Squamous carcinoma of esophagus (H)	34.9	5.1	6.8
5. Gastric adenocarcinoma (H)	49.0	4.1	12.0
6. Adenocarcinoma of rectum (H)	35.3	4.0	8.8
7. Adenocarcinoma of rectum (H)	46.0	3.6	12.7
8. Adenocarcinoma of stomach (H)	28.5	4.7	6.1
9. Adenocarcinoma of stomach (H)	41.5	4.0	10.4
10. Cancer of breast (H)	28.5	5.4	5.3
11. Cancer of breast (H)	27.5	6.1	4.5
12. Cancer of stomach (H)	33.0	2.4	13.8
13. Cancer of breast (H)	39.0	4.0	9.8
14. Cancer of kidney, 15 days after operation (H)	57.0	2.9	19.7
15. Cancer of kidney (H)	56.8	3.1	18.3
16. Fibrosarcoma with pulmonary metastases (H)	63.5	3.6	17.6
17. Squamous carcinoma of tongue (H)	17.5	3.6	4.9
18. Cancer of thyroid with metastases (H)	52.5	4.5	11.7
19. Adenocarcinoma of pancreas, probably residual carcinoma	32.9	2.9	11.4
20. Carcinoma of pancreas	35.9	2.4	14.9
21. Carcinoma of rectum, 25 days postoperative	47.2	2.5	18.9
22. Same as 21, 31 days postoperative	50.5	2.8	18.0
23. Cancer of lip	64.5	3.6	17.9
24. Cancer of lip	65.0	3.8	17.1
25. Cancer of lip	57.0	3.1	18.4
26. Carcinoma of rectum	73.0	2.3	31.8
27. Carcinoma of rectum	57.5	3.0	19.2
28. Carcinoma of stomach	41.0	2.7	15.2
29. Spine, metastases cancer, 29 days postoperative	52.2	2.9	18.0
30. Same as 29	45.0	3.1	14.5
31. Same as 30	44.5	2.9	15.3
32. Same as 31, 37 days postoperative	47.5	3.0	15.8
33. Cancer of bowel	37.0	2.4	15.4
34. Carcinoma of stomach	60.5	3.4	17.8
35. Carcinoma of esophagus	26.5	5.3	4.82
36. Cancer of kidney	66.5	2.3	28.9
37. Cancer of breast	50.1	5.3	9.4
38. Adenocarcinoma of left colon with metastasis	63.9	3.95	16.2
39. Early cancer, tiny lesion on breast	40.5	6.23	6.5
40. Cancer of colon	40.2	not done	—
41. Squamous cell carcinoma of esophagus (H)	35.0	not done	—
42. Carcinoma of bladder, one day postoperative (H)	32.7	not done	—
43. Adenocarcinoma of rectum (H)	39.4	not done	—
44. Adenocarcinoma of rectum (H)	38.5	not done	—
45. Adenocarcinoma of rectum, recurrent (H)	20.0	not done	—
46. Cancer of bladder	29.0	not done	—
47. Adenocarcinoma of stomach with metastasis (H)	55.9	not done	—
48. Cancer of lung	36.2	not done	—
49. Small carcinoma of breast	31.7	not done	—
50. Adenocarcinoma of stomach	53.9	not done	—
51. Same as 50, 8 days postoperative	60.8	not done	—
52. Abdominal tumor	38.1	not done	—
53. Adenocarcinoma of sigmoid colon	44.6	not done	—
54 to 91. Diagnosis not available	25.0 to 70.2	2.2 to 5.0	8.22 to 23.6
92 to 96. Diagnosis doubtful regarding cancer	25.0 to 45.5	2.2 to 4.6	8.1 to 20.7

° mg. cysteine per 100 cc. serum
(H) histologic

allow definite conclusions, it is to be noted that this marked difference in RSH between cancerous and other pathological sera might yield a more specific test for cancerous sera than the h_{30} value.

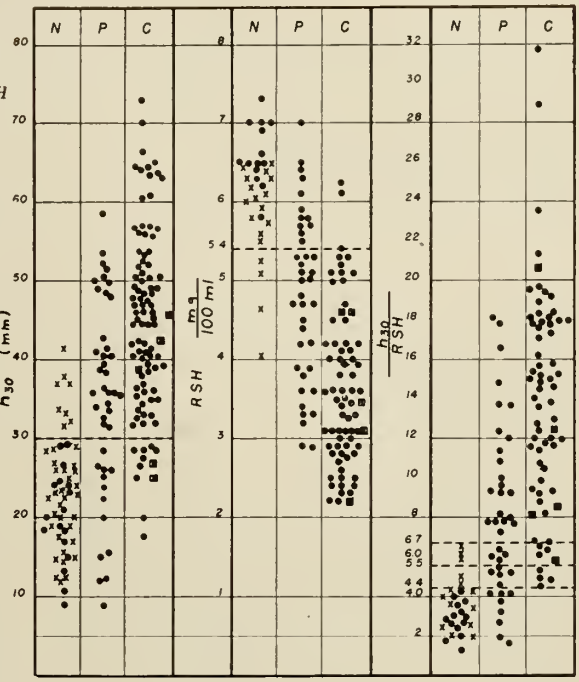

Fig. 3. Graphic presentation of h_{30}, RSH and h_{30}/RSH for Normal (N), Noncancerous Pathological (P) and Cancerous (C) sera. × Normal sera obtained from Cancer Detection Center. ⊠ Clinical diagnosis doubtful with regard to cancer.

A comparison and evaluation of the two tests can best be obtained from a graphic presentation of the data as given in figure 3.

Considering normal and cancerous sera it is seen from figure 3 that values greater than 30 in h_{30}, smaller than 5.4 in RSH, and greater than 5.5 in h_{30}/RSH are indicative of cancer. An inspection of these figures shows that the extent of overlapping of normal and cancerous sera is markedly smaller for the RSH and h_{30}/RSH values than it is for h_{30}. Taking a value smaller than 5.4 for RSH (expressed as mg. cysteine per 100 ml. serum) as indicative for cancer, it is found that 12 per cent of the normal sera (32 cases) give a positive cancer test while only 3 per cent of the cancerous sera (72 cases) give a negative test. Taking a value of h_{30} greater than 30 as indicative of cancer it is found that 15 per cent of 55 normal sera give a positive cancer test and 12 per cent of 96 cancerous sera a negative test. Details concerning abnormal test results are given in table V. It is seen from section A of this table that two of the "normal" sera with RSH values < 5.4 give a positive and one a negative Brdicka test. The sample with the negative Brdicka test was obtained from a person with suspected cancer, however an operation indicated no cancer. Two of the other three sera, obtained from the Cancer Detection Center, apparently were not normal; the clinical diagnosis (arteriosclerosis and allergic rhinitis) may account for the low RSH–values. It is interesting to note from section B of table V that in three cases

TABLE IV

AVERAGE VALUES OF h_{30}, RSH, AND h_{30}/RSH

Sera	h_{30} Number of cases	h_{30} Mm.	h_{30} Standard deviation	h_{30} μA	h_{30} $\mu A/m^{2/3} t^{2/3}$
"Normal" (no disease or suspected disease)	17	20.2	6.0	15.2	4.46
"Normal" from Cancer Detection Center	38	24.4	7.9	18.3	5.37
Pathologic noncancerous	42	36.8	12.2	27.6	8.10
Cancer	91	38.2	11.7	28.6	8.40
Clinically doubtful regarding cancer	5	35.8	–	26.9	7.90

Sera	RSH Number of cases	RSH Mg. per 100 cc.	RSH Standard deviation	h_{30}(mm.)/RSH RSH
"Normal" (no disease or suspected disease)	14	6.6	0.33	2.86
"Normal" from Cancer Detection Center	14	5.8	0.48	3.96
Pathologic noncancerous	39	5.1	1.01	7.60
Cancer	67	3.8	0.97	13.0
Clinically doubtful regarding cancer	5	3.6	–	11.1

of breast cancer all the RSH-values were negative while two out of three values of h_{30} were negative. All other sera obtained from patients with breast cancer gave positive RSH- and h_{30}-values (see table II). Section C of table V gives eight cancerous sera with negative (no cancer) h_{30}-values while four out of six of these sera give positive RSH-values.

Our present results show that the amperometric determination of the sulfhydryl content of blood sera as a clinical routine test for the detection of cancer generally gives more conclusive results than the polarographic test (h_{30}). Moreover the RSH test can be carried out rapidly with very simple equipment. The limitation of both tests from a diagnostic view is that in our study 69 per cent of the pathological noncancerous sera gave a positive h_{30} and a positive RSH value.

From figure 3 it is seen that the value of h_{30}/RSH allows more definite conclusions than either value alone. The following classification can be made: value of h_{30}/RSH >6.7 is pathological, of 4.4 to 6.7 is uncertain, and a value < 4.4 is normal. An analysis of the experimental figures on this basis is given in table VI. It is seen that with this classification none of the 28 normal sera investigated give pathological values and none of the 67 cancerous sera give normal values. The uncertain cases are 18 and 10 per cent for normal and cancer cases respectively. An inspection of table V indicates that all the overlapping cases with the exception of one (operation for cancer negative) are in the "uncertain" class. Considering the noncancerous pathological sera, it is found that somewhat more than half of these give positive values while the other

TABLE V

"ABNORMAL" VALUES OF RSH AND h_{30} OBTAINED IN NORMAL AND CANCEROUS SERA

A. "Normal" sera with RSH $<$ 5.4 (from Cancer Detection Center)

RSH	h_{30}	h_{30}/RSH	Clinical diagnosis
4.03	not done	–	arteriosclerosis
4.65	11.7	2.52	suspected cancer but operation indicated no cancer
5.1	33.8	6.62	not available
5.3	32.2	6.11	allergic rhinitis

B. Cancerous sera with RSH $\geq$ 5.4

Reference to number in table III	RSH	h_{30}	h_{30}/RSH	Clinical diagnosis
39	6.23	40.5	6.5	early cancer (tiny lesion on breast)
11	6.1	27.5	4.5	breast cancer
10	5.40	28.5	5.3	breast cancer

C. Cancerous sera with h_{30} $<$ 30 mm.

Reference to number in table III	RSH	h_{30}	h_{30}/RSH	Clinical diagnosis
17	3.6	17.5	4.9	cancer of tongue
45	not done	20.0	–	cancer of rectum
–	not done	25.0	–	diagnosis not available
35	5.3	26.5	4.82	cancer of esophagus
11	6.1	27.5	4.5	cancer of breast
10	5.4	28.5	5.3	cancer of breast
2	4.2	28.5	6.8	cancer of neck
8	4.7	28.5	6.1	cancer of stomach

TABLE VI

CLASSIFICATION OF 134 BLOOD SERA ON THE BASE OF THE RATIO h_{30}/RSH

Cases	Number of cases tested	Pathologic value > 6.7° Number	Pathologic value > 6.7° Per cent	Uncertain value 4.4 to 6.7° Number	Uncertain value 4.4 to 6.7° Per cent	Normal value < 4.4° Number	Normal value < 4.4° Per cent
Normal	28	none	0.0	5	18	23	82
Cancer	67	60	90	7	10	none	0.0
Pathologic noncancerous	39	22	56	9	23	8	21

° Expressing h_{30} as $\mu A/m^{2/3} t^{2/3}$ these values are: pathologic: > 1.47, uncertain: 0.97 to 1.47, normal: < 0.97.

half is about equally divided between the uncertain and normal groups.

There is no apparent genetic relation between the polarographic and amperometric tests. Studies on different fractions of serum proteins and also on the rate of hydrolysis and digestion of proteins are planned in order to arrive at a more specific differentiation between normal and cancerous sera.

SUMMARY

The polarographic serum reaction proposed by Brdicka for the detection of cancer has been studied critically and a modified procedure denoted as the "centrifugate test" is proposed. This test, giving the "h_{30}" value and the amperometric sulfhydryl (RSH) titration, has been applied to normal, cancerous and other pathological sera.

An analysis of the results obtained with 55 normal, 96 cancerous, and 42 noncancerous pathological sera indicates that the sulfhydryl titration as a routine test is preferable to the polarographic test in the differentiation between normal and cancerous sera.

A value smaller than 5.4 for RSH (expressed in mg. cysteine per 100 ml. of serum) and a value greater than 30 mm. for h_{30} (corresponding to 8.8 $\mu A/m^{2/3} t^{2/3}$) indicates cancer. An analysis of the results shows that 12 per cent of normal sera gives a positive (cancer) RSH test and 15 per cent a positive h_{30} test. Of the cancerous sera 3 per cent give a negative RSH test and 12 per cent a negative h_{30} test.

Neither test is specific for cancer, since many pathological noncancerous sera give positive cancer tests.

It is found that the ratio h_{30}/RSH allows more definite conclusions than either test alone. On the basis of this ratio three classes can be distinguished, ratio h_{30} ($\mu A/m^{2/3} t^{2/3}$/RSH > 0.97 is normal, ratio between 0.97 and 1.47 doubtful, and ratio greater than 1.47 is cancer or pathological noncancer. With this classification it is found that none of the normal sera investigated gives a pathological value and none of the cancerous sera gives a normal value, while noncancerous pathological sera are about equally divided between the cancer group (56 per cent) on the one hand, and the uncertain (23 per cent) and normal (21 per cent) group on the other hand.

This investigation was supported by a research grant from the National Cancer Institute, United States Public Health Service. Acknowledgment is also made to Dr. O. H. Wangensteen, chairman, Dr. G. E. Moore and Dr. D. State, members of the department of surgery of the University of Minnesota for their cooperation in making blood samples available. The authors wish to express their special appreciation to Dr. G. E. Moore who provided the clinical information given in tables II and III.

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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.*

Clinicopathological Conference

Minneapolis Veterans Hospital°

Edited by JAMES F. HAMMARSTEN, M.D.

CASE 14

PRESENTATION OF CASE

A 53-year-old mail carrier was admitted on June 20, 1951, because of chest pain.

On April 12, 1951 he awoke with pain in the left shoulder. The pain was constant, boring, and aggravated by movement of the arm. Because the pain persisted for 48 hours, he consulted a physician. An extensive investigation was conducted including x-ray studies of the chest, gallbladder and gastrointestinal tract. He was advised to return but failed to do so since the pain completely disappeared by April 16.

He was well until June 13 when he was awakened by pain in the left shoulder. A heating pad afforded some relief but the pain continued until June 15. He then developed left lateral chest pain which was aggravated by deep breathing and movements of the trunk. He was hospitalized but the chest pain continued. X-ray studies of the chest disclosed a tumor and he was transferred to this hospital.

He also complained of excessive fatigue for six months. In 1931 he had a febrile disease with cough, nuchal rigidity and spontaneous recovery. The family history was not significant.

Physical examination was negative. The vital capacity was 4.4 liters.

The temperature was 98.4° F., the pulse rate 72 per minute, and the blood pressure 120 mm. Hg systolic and 70 diastolic.

The hemoglobin was 14.3 gm. per 100 ml. and the white blood cell count 7200 per mm.^{3} with 82 per cent neutrophils, 12 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils. The erythrocyte sedimentation rate was 25 mm. in one hour. A urinalysis was normal. A blood Kahn was negative. The blood urea nitrogen was 18 mg. per 100 ml., and the plasma protein 6.6 gm. per 100 ml. with 4.9 albumin and 1.7 globulin. The stool was negative for blood, ova, and parasites. An electrocardiogram was normal.

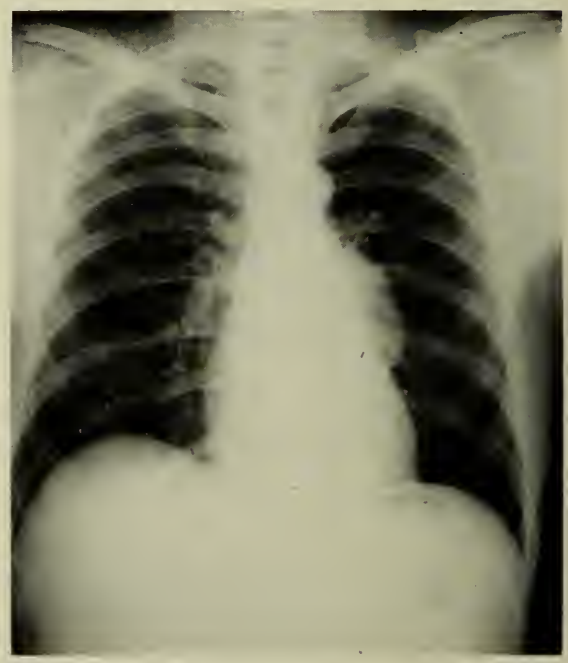

Fig. 1. X-ray film of the chest showing a mass in the left hilus.

X-ray films of the chest showed a lobulated mass located in the anterior mediastinum on the left (figures 1, 2 and 3). Fluoroscopy demonstrated the mass with slight pulsations which appeared to be transmitted rather than expansile.

Bronchoscopy was negative. Three examinations of the sputum and bronchial aspirations failed to reveal tumor cells. The first strength tuberculin test was negative and the second strength strongly positive.

On July 2, 1951 an operation was performed.

DISCUSSION

DR. JOHN LA BREE°: From the history and physical examination we get little help and must turn to the x-ray studies. When we consider the x-ray films certain questions are raised. Is this shadow vascular? Is it mediastinal Is it in the parenchyma of the lung? Is it benign or malignant?

°Published with approval of Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

°Assistant clinical professor, University of Minnesota and internist at the St. Louis Park Medical Center.

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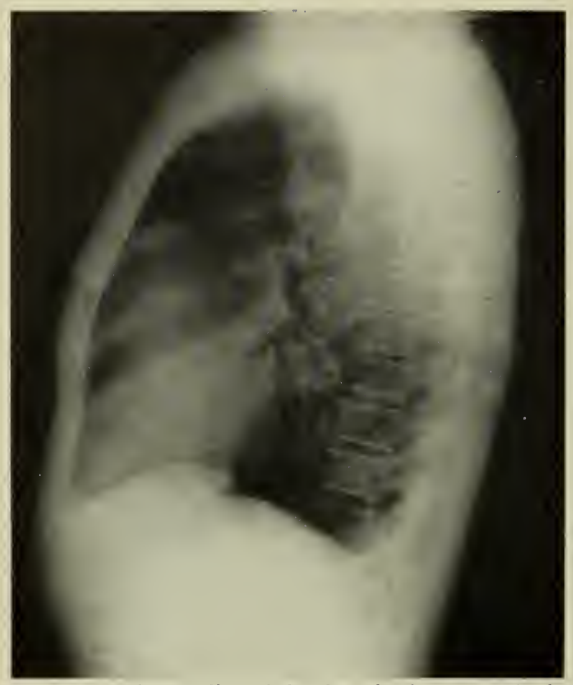

Fig. 2. Lateral x-ray films of the chest showing a mass in the anterior mediastinum.

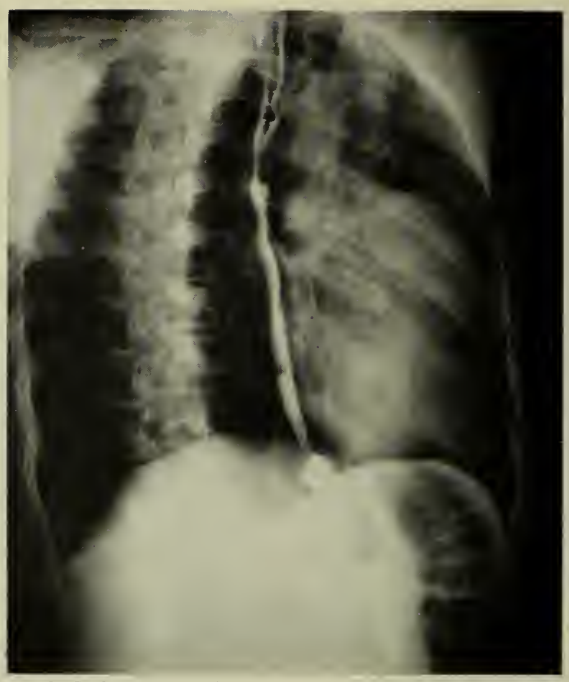

Fig. 3. Right anterior oblique view of the chest showing the mass.

From the fluoroscopic reports and the x-ray films we can exclude a vascular lesion with a fair degree of certainty. The x-ray films suggest that it is mediastinal. Bronchoscopy failed to reveal involvement of the bronchi. I believe the mass is in the anterior mediastinum.

We can not answer the last question unequivocally. We must consider the lymphoma group. If it were a lymphoma, I would expect to find other manifestations, such as lymphadenopathy, splenomegaly, and abnormal hematologic values. If this were metastatic carcinoma, I would expect to find some evidence for a primary lesion by history or examination, and again abnormal hematologic values.

What needs most serious consideration is an isolated lesion of the mediastinum. The most common lesion of the anterior mediastinum is one of the teratoma group, such as a dermoid. Less common is a neurofibroma which usually occurs in the posterior mediastinum.

Another lesion of the anterior mediastinum is a thymoma. That diagnosis is intriguing in view of the fatigue. Thymomas are not infrequently associated with myasthenia gravis. Unfortunately the man does not have diplopia or dysphagia or any of the other early signs of myasthenia gravis.

I believe the lesion in this case is most likely a dermoid and my second choice is a thymoma.

DIAGNOSES

Clinical diagnosis: Pericardial cyst or bronchial cyst or teratoma or thymoma.

Dr. La Bree's diagnosis: Dermoid or thymoma.

Anatomical diagnosis: Malignant lymphoma, lymphosarcoma type, originating in the region of the thymus.

PATHOLOGICAL DISCUSSION

DR. GLEASON: The operation was, of course, a thoracotomy. The tumor was 11 cm. in diameter and was adhered to the pericardium. The tumor was resected. The cut surface of the tumor was solid, soft, white and had areas of necrosis. It was a lymphoma so far as we could tell from histological examination. Nothing resembling the thymus gland was seen. This is what is frequently called a malignant thymoma. The tumors are limited in the early stage to the site of the thymus, but histologically are some type of malignant lymphoma.

The patient developed jaundice following surgery. Jaundice persisted for nine weeks. He had two courses of x-ray therapy, developed inanition and died.

At autopsy there was local recurrence of the tumor. The tumor surrounded the aorta. There were metastatic lesions in the mediastinal nodes, liver, and right kidney. The lesions resembled the resected tumor histologically. It would correspond better with a lymphosarcoma than anything else.

DR. E. T. BELL: This tumor is a lymphosarcoma. The position suggests that it grew in the thymus. If you believe in malignant thymomas, this is one. If you want real proof that this originated from the thymus gland, it is lacking. Most of the malignant thymomas reported in the literature are like this. There is nothing to prove thymoma except the apparent origin. The only safe thing to say is that it is a malignant lymphoma of the lymphosarcoma type. It might have originated from the thymus but nobody can prove it.

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News Briefs . . .

North Dakota

Recommendations that plans for the two year medical school at the University of North Dakota be carried out and that no new projects be undertaken were made in a resolution by the North Dakota state medical center advisory council at the meeting at Grand Forks on June 16. This resolution was in opposition to a senate bill of the 1953 legislature, which directed the board of higher education to retain a sufficient portion of medical center funds to permit the establishment of a third year course in medicine not later than 1955 and a fourth year course not later than 1956.

In the resolution, the council expressed doubt that there was sufficient income to provide for the operation of the two year school and in addition accumulate the amount required for a third and fourth year course within the time specified. They also recommended that the board go ahead with careful investigations and plans and be prepared to present to the 1955 legislative session a complete report as to available funds and requirements for the establishment of the third and fourth year medical courses.

* * *

Construction of a 50-bed addition to the Good Samaritan hospital at Williston is in the planning stage. A financial drive is slated to begin early in October, and architectural plans are being drawn.

* * *

The North Dakota-Manitoba Urological Society held its meeting at Minaki Lodge, Minaki, Ontario, on June 12. The following officers were elected to serve during the coming year: Dr. Joseph Sorkness, Jamestown, president; Dr. John Sandmeyer, Grand Forks, vice president; and Dr. L. F. Pine, Devils Lake, secretary-treasurer. The society was recently guest to the Canadian Urological Association meeting held at Minaki.

Dr. Russell O. Saxvik, North Dakota health officer, has been appointed superintendent of the Jamestown state hospital. Dr. Saxvik succeeds Dr. A. M. Fisher who retired on the first of July.

* * *

Dr. Herman E. Hilleboe, a native of Westhope, North Dakota, was awarded an honorary degree by the University of Rochester. Dr. Hilleboe is commissioner of health for the New York state public health department and formerly served as medical director of the USPHS tuberculosis division and directed tuberculosis control in Minnesota.

Minnesota

Three grants for polio research projects, totaling $113,000, have been awarded to the University of Minnesota by the Foundation for Infantile Paralysis. One grant of $83,646 will be directed by Dr. Jerome T. Syverton, professor of bacteriology and immunology, toward development of a rapid laboratory test for polio diagnosis. Dr. A. B. Baker, professor of neurology, will have supervision of another grant of $24,511 to expand studies of brains and spinal cords from more than 100 fatal cases of bulbar polio. Under a grant of $5,671, Dr. Gaylord W. Anderson, Mayo professor of public health, will continue a careful analysis of data collected on several thousand polio patients during the Minnesota 1946 epidemic.

* * *

A clinic for diagnosis of multiple sclerosis was opened July 1 at University of Minnesota hospitals. The 1953 Minnesota legislature appropriated $10,000 a year for this year and next to the Minnesota chapter of the National Multiple Sclerosis society for establishment of the clinic, which will be under the direction of Dr. A. B. Baker, head of the neurology division in University hospitals.

American College Health Association News . . .

Dana L. Farnsworth, M.D.

Dr. Dana L. Farnsworth, *Medical Director, Massachusetts Institute of Technology, assumed the office of President of the American College Health Association at the end of the Columbus meeting on May 2, 1953. In addition he will be chairman of the Fourth National Conference on Health in Colleges, which meets in conjunction with the American College Health Association at the Hotel Statler, New York City, May 5, 6, 7, and 8, 1954. His main interests in the field of student health include the development of health programs in colleges which will serve to make students aware of their possible roles as community leaders in maintaining high health standards and the application of psychiatry to education.*

The sixteenth annual meeting of the Michigan College Health Association was held at General Motors Institute, Flint, on May 22, 1953. Thirty-one people were present representing nineteen colleges and universities. Dr. Max Durfee, immediate past president of the American College Health Association, was a guest. Mrs. Opal Thorpe sent in a summary of the meeting.

Miss Minetta Nicolai of the Michigan Tuberculosis Association gave a brief summary of the status of tuberculosis in Michigan. She reported that the number of deaths from tuberculosis for 1952 was 378 less than for 1951 but that the number of new cases found was no less, which would indicate that the decline in deaths was more evidence of effectiveness of treatment than a decline in the disease itself.

Officers elected for the year 1953-54 are: President—Dr. Irvin W. Sander, Wayne University, Detroit; vice-president—Dr. Olga Sirola, Michigan State Normal College, Ypsilanti; secretary-treasurer—Mrs. Marion L. Kelly, Jackson Junior College, Jackson.

The Journal Lancet

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Pulmonary Hypertension*

LESTER E. WOLD, M.D.

Fargo, North Dakota

SOME INVESTIGATORS have expressed doubt that pulmonary hypertension exists as a primary condition. We would like to present a patient in whom we feel such a diagnosis is reasonably secure. In recent years, Edwards[1] has done much to clarify the structural changes that occur within the lung in pulmonary hypertension and he offers the following classifications: (1) impaired pulmonary venous flow, (2) disproportion between pulmonary blood flow and the capacity of the pulmonary bed, (3) common ventricular projectile force for both the systemic and the lesser circulation in the absence of pulmonary stenosis. To this classification we would add (4) essential pulmonary hypertension.

The first group includes mitral stenosis, mitral insufficiency, aortic stenosis, left heart failure, and mediastinitis. The second group includes those pathologic situations in which there is either a decreased pulmonary bed or an increased pulmonary flow. Edwards reports an interesting case of a patient who had widespread clinical pulmonary hypertension and at necropsy was shown to have extensive mediastinitis which mechanically obstructed the venous return from four of the five lobes of the lung. In studying the structural changes in the lung, he reported medial hyperplasia and intimal thickening of the muscular arteries in the lobes in which the venous return was obstructed. In the one unobstructed lung, the pulmonary vessels appeared normal. Edwards also reminds us that in the presence of a normal pulmonary vascular bed the pulmonary pressure may be elevated if the flow is exceeded four times normal. The third category includes a wide variety of the congenital anomalies. In this wide variety of conditions, the same pathologic findings have been noted. The previously mentioned medial thickening and intimal proliferation have been observed in all categories. In addition, atherosclerosis of the larger or elastic pulmonary vessels has been described.

The significant conclusions by Edwards and others is that in this wide variety of cardiovascular diseases, the same intrapulmonary pathology is noted. The implication is that if search is diligent enough, one of the first three mentioned categories would be encountered in everyone with pulmonary hypertension. Inasmuch as all of these possibilities have been reasonably excluded as primary diseases, we feel our patient represents a case of essential pulmonary hypertension.

Case 121166, Mrs. D. L. S., age 24, female, referred to the Department of Internal Medicine because of cough, chest pain, and dyspnea of two weeks' duration. Past history revealed normal childhood illnesses, but no history of scarlet fever or rheumatic fever. Three previous pregnancies were uneventful.

First seen on November 1, 1951, at which time the patient stated she had felt well except for exertional dyspnea, a hacking cough, and intermittent, sharp bilateral chest pain with epigastric soreness of two weeks' duration. The children had had upper respiratory infections at home. No ankle edema was noted. The blood pressure was 80/60. There was a grade II systolic apical

LESTER E. WOLD *graduated from Rush Medical College in 1938, received his M.S. in internal medicine at the University of Minnesota, and did graduate work at the Mayo Foundation. He is on the staff of St. Lukes Hospital, Fargo, and is a member of the first district medical society, American Board of Internal Medicine, and an associate in the American College of Physicians.*

*Read before the regional meeting of the American College of Physicians, Grand Forks, North Dakota, September 13, 1952.

murmur. The pulmonic second sound was accentuated and louder than the aortic second sound. Routine studies were advised along with a fluoroscopic examination of the heart and electrocardiographic studies.

She returned two days later with the story of having become extremely dyspneic and fainting after walking upstairs. Laboratory data revealed negative urinalysis, a sedimentation rate of 2 mm. in one hour, hemoglobin 13 gm., and white count 11,200. Routine chest ray showed cardiac enlargement with mitral configuration. Cardiac fluoroscopy revealed prominence of the pulmonary artery but no enlargement of the left auricle. There was no notable congestion of the intrapulmonary vessels. Conclusions reached were that findings were not those of mitral disease with failure. Electrocardiographic tracings revealed a right axis deviation with a rate of 110, a normal PR interval.

During the course of the illness, hoarseness became prominent; exertional dyspnea became more pronounced; and tachycardia persisted. She was referred elsewhere for cardiac catheterization. While being studied she had a convulsive seizure after which she looked very pale and weak for some hours. The blood pressure during this period averaged 80 systolic and 65 diastolic. Her catheterization data indicated a pulmonary hypertension which was greatly increased by exercise, but the pressure obtained by wedging the catheter in a pulmonary artery, so-called wedge pressure, was normal. The cardiac output was low. She had a mild generalized convulsive seizure after the catheterization and developed post-catheterization thrombophlebitis of the right arm veins. She was placed on a cardiac regimen of restricted activity and digitalized. She made modest improvement, but in January her dyspnea became more prominent. Her liver enlarged. She developed sacral and leg edema. She responded fairly well to mercurial diuretics. She was hospitalized on two occasions and given anticoagulants. Her anasarca increased. Her liver enlargement progressed. She developed a right hydrothorax and died May 2 of cardiac failure, six months after the onset of her symptoms.

Necropsy revealed a bilateral hydrothorax. The heart was enormously enlarged and almost completely filled the thoracic cage. The right ventricle was dilated to many times its normal size. The wall measured 20 mm. in thickness. The mitral valves and chordae tendons appeared normal. The aorta cusps were normal. The pulmonary veins were normal in size and appearance. The pulmonary artery was dilated to two times normal size throughout. There were several old and recent pulmonary infarcts measuring up to 5 cm. in diameter, the larger of which had undergone central liquefaction. The microscopic picture revealed pronounced medial thickening of the muscular arteries with intimal proliferation. Atherosclerosis of the elastic arteries was prominent. There were many old and recent thrombi, some of which had recanalized. No evidence of pelvic or ileo-femoral thrombosis was noted.

CONCLUSION

A case of pulmonary hypertension has been reported. We feel that those pathologic situations which are generally accepted as causing pulmonary hypertension have been adequately excluded and that the case reported represents a case of primary pulmonary hypertension.

REFERENCE

1. Jesse E. Edwards, personal communication.

The incidence of massive pulmonary embolism is much greater for individuals with early thromboembolism, probably because sufficient time does not elapse for the long clot to become firmly attached to a peripheral vein wall.

Shock, hypotension, or relative hypotension precedes nearly all early episodes of postoperative pulmonary embolism, finds Harry A. Davis, M.D., of the College of Medical Evangelists, Los Angeles. Thromboembolisms occurring in the lung within forty-eight hours after an operation, accidental injury, or hemorrhage have an extremely rapid course and a high incidence of massive embolic occlusion of the main pulmonary artery.

The patients are usually at least 50 years of age. The incidence is higher in elderly persons because of the difficulty in reestablishing normal blood flow after hypotension and also because of the more frequent saccular dilatation of the veins with age.

Most of the emboli originate in the leg veins, since the venous pathways are longer, develop a larger cross-sectional area with age, and usually have more severe and prolonged vasoconstriction.

Harry A. Davis: Studies in thrombo-embolic disease: 1. acute early pulmonary embolism (within forty-eight hours) following surgical operation, trauma, and hemorrhage. Ann. Surg. 137:356, 1953.

A Study of Labor Induction*

FRANK A. HILL, M.D.
Grand Forks, North Dakota

In the not too distant past, the induction of labor was reserved for those cases in which premature labor was deemed advisable because of a small pelvis. At the present time, however, indications for the precipitation of labor have been increased to include certain of the toxemias and some of the hemorrhage group, as well as some diabetics. Acceptance of induction is not as widespread for the cardiac, the tuberculous patient, the so-called postmature group, and the borderline pelvic cases. The elective induction of labor for the convenience of the patient or doctor received impetus during the war years largely because of overcrowding and shortage of hospital facilities, the harassment of the overworked physician, and transportation difficulties. To these factors influencing elective induction of labor, seasonal conditions and long distances between the patient's home and the hospital, as found in North Dakota, have been added.

Some believe induction for the convenience of the patient is never indicated,[1] and others hold that the precipitation of imminent labor is a justifiable procedure.[2]

The increasingly available hospital facilities and the lessening of the individual physician work load since the end of the war, have not resulted in any noticeable decrease in the number of labor inductions. It was felt that a study of the practice of labor induction at the present time, in a typical North Dakota city serving urban and rural population, might be of value.

MATERIAL

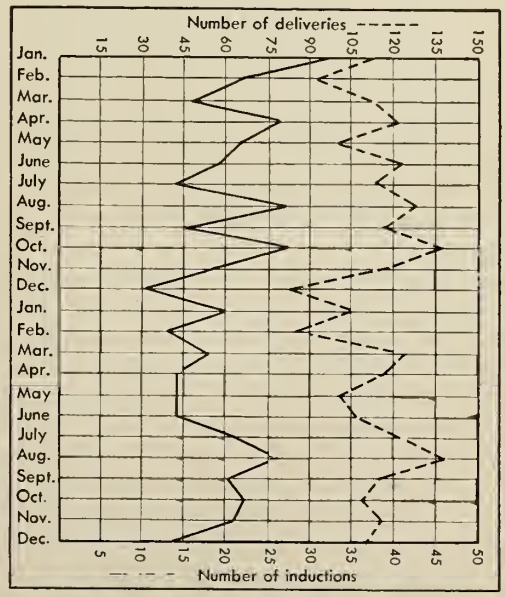
The material for this study was obtained from the hospital records of the two private general hospitals in Grand Forks, North Dakota, covering the labor inductions of a two-year period — July 1, 1950, through June 30, 1952. The two hospitals have a combined maternity bed count of 38, have the same attending medical staff, and same staff regulations. There are 15 physicians practicing obstetrics, 3 of whom confine their practices to obstetrics and gynecology. Since there is but little difference in the obstetrical services of the two hospitals, the respective figures have been combined for the purpose of this study.

During the period July 1, 1950, through June 30, 1952, there were 2,713 mothers delivered in the two hospitals; 465 or 17.3 per cent of these had induced labors. There were 353 multiparous patients and 112 primiparous patients. Of this series of 465 inductions, 293 or 63 per cent were from the urban area of Grand Forks and 172 or 37 per cent from the rural area. Failed inductions were not included.

RESULTS

It was thought it might be of interest to graph the number of monthly deliveries and inductions to show seasonal influence (table 1). Usually the incidence of inductions varies proportionally with the number of deliveries with but one winter month influencing the curve relationship.

TABLE 1
MONTHLY DELIVERIES AND INDUCTIONS



FRANK A. HILL, *a graduate of Rush Medical College in 1940, is chief of obstetrics and gynecology at St. Michaels Hospital, Grand Forks, and is on the staff of Deaconess Hospital, Grand Forks. He is a member of the Central Association of Obstetricians and Gynecologists, American Academy of Obstetrics and Gynecology, North Dakota Society of Obstetrics and Gynecology, is a fellow in A.C.S., and certified by American Board of Obstetrics and Gynecology.*

*Presented before the North Dakota Society of Obstetrics and Gynecology, September 12, 1952.

The indications for induction are listed in table 2. The classification convenience of the patient includes those so designated, those induced because of the rural factor, and a large group in whom no indication was given, and perusal of the records failed to reveal other possible reasons. This convenience group comprised 68 per cent of the inductions.

TABLE 2
INDICATIONS FOR THE INDUCTION OF LABOR

Indication	*No.*	*Indication*	*No.*
1. Postmaturity	50	10. Rh sensitization	3
2. Toxemia	49	11. Polyhydramnios	3
3. Short labors	8	12. Twins	3
4. Heart disease	7	13. Diabetes	2
5. Varicose veins	5	14. Premature rupture of membranes	2
6. Placenta praevia	5	15. Convenience of patient	316
7. Abruptio placenta	4	Total	465
8. Borderline pelvis	4		
9. Pyelitis, recurrent	4		

The method of labor induction varied. Practically all patients received castor oil or a soapsuds enema or both initially. The most frequently employed method was the use of intramuscular Pituitrin or Pitocin, being used in 174 or 37 per cent of this series of 465, in total dosage ranging from 1 minim to 3.6 cc. The most widely used dosage was 2 minims every one-half hour for 5 to 6 doses and the series repeated until labor ensued or additional measures employed. The next most frequent procedure was amniotomy in addition to intramuscular Pituitrin, the time of amniotomy varying in the course of the induction. This combination of amniotomy and intramuscular Pituitrin was used in 98 or 21 per cent of the series. Next in order was the use of amniotomy alone, being the procedure of choice in 63 or 13.7 per cent. The combined use of Pituitrin intramuscularly and intravenously was employed in 45 or 9.6 per cent, with total combined dosage ranging to 7 cc. in a forty-eight-hour period. The usual method was the initiation of intramuscular Pituitrin followed by 1 cc. of Pituitrin in 500 cc. diluent given intravenously in a three- to six-hour period. Amniotomy was added to this combination in 11 cases, and a Vorhees' bag was inserted in 1 patient in addition to the aforementioned three procedures. Intravenous Pituitrin alone was employed in 29 or 6.2 per cent of the series under study, with dosages ranging from less than 1 cc. to 6 cc. given over a period of sixty hours. Quinine was used alone twice and in conjunction with Pituitrin in an additional 12 cases; the quinine dosage being 12 to 15 gr. in a fifteen-hour period. Castor oil alone was used in 22 cases. Labor was induced in 3 patients by the use of the catheter and pack method, in 1 of whom Pituitrin also was used.

The determination of the latent period between induction and onset of labor could not be obtained from the records; in some instances the induction was carried to the "crowning stage." Likewise, the actual duration of labor could not accurately be obtained in all cases. The average labor of those cases that could be obtained was shortened from the usually accepted averages, being seven hours and fifteen minutes in the primiparous group and four hours and forty minutes in the multiparous group.

The methods of delivery are listed in table 3, the incidence of the various methods generally following the over-all figures for this period.

TABLE 3
METHODS OF DELIVERY

Method	*Number*	*Per cent*
Low forceps	251	54.0
Spontaneous	182	39.0
Mid forceps	17	3.9
Breech	10	2.1
Cesarean section	3	0.6
Version and extraction	2	0.4
Totals	465	100.0

The indications for cesarean section were hemorrhage in one, and failure of the presenting part to descend, after a trial, in the other two. The version and extractions were necessitated by prolapse of the cords.

COMPLICATIONS

No maternal deaths occurred in this series. The maternal morbidity was 37 cases or 8 per cent, as compared to an over-all maternal morbidity for this two-year period of 5.1 per cent. The causes of morbidity were listed as urinary tract infection in 15, upper respiratory infection in 6, gastroenteritis in 5, 2 patients developed pneumonia, and cause not known or listed in 9.

There were 11 patients diagnosed as having postpartum hemorrhage in this inducted group, 1 due to laceration, 1 to retained cotyledon, and the remainder attributed to uterine atony. Nine of these hemorrhages occurred in the convenience group. The number of postpartum hemorrhages in the 2,713 mothers delivered in this two-year period was 33.

INFANT RESULTS

There were 6 stillbirths in this series of 468 babies delivered of 465 mothers, 1 being an anencephalic, 1 erythroblastotic, 1 following abruptio placenta, and 3 in the toxemic group of

patients. Nine of the babies delivered were premature, the smallest being just under 2,000 gm. Four of these prematures were delivered after induction of labor for convenience. One premature baby died; the mother of this baby was a toxemic patient. There were 3 neonatal deaths, 1 due to spina bifida and meningocele, and 2 attributed to atelectasis. One of these 2 deaths followed induction for toxemia; the baby weighed slightly over 3,000 gm. The other occurred after induction for convenience and weighed 2,700 gm. One newborn showed evidence of severe intracranial bleeding after a difficult breech delivery in a primagravida, and 1 exhibited quite pronounced atelectasis. However, both babies survived. Eliminating the premature and congenital deformity deaths, this gives a neonatal mortality rate of 0.4 per cent for this series of 465 induced patients. This is a slightly lower figure than the 0.5 per cent corrected neonatal figure for the entire number of patients delivering in this two-year period.

DISCUSSION

In this series of cases, an attempt has been made to evaluate the factors concerned in the induction of labor as practiced during a recent two-year period in a typical North Dakota center. Slightly over 17 per cent of all deliveries were found to follow induced labor, with 68 per cent of these being for the convenience of the patient or doctor. From this study, season and rural status do not appear to be big factors.

The most frequently employed type of induction involved the use of Pituitrin or Pitocin in dosages generally exceeding the accepted totals. Rupture of the uterus, anuria, and death have been attributed to Pituitrin in doses smaller than employed generally in this series. Rupture of the uterus has been noted in doses as low as 2 to 3 minims.[1] Pituitrin shock and sensitivity are known complications. None of these, however, were noted in this series. The use of more than one type of induction procedure, in some instances, would be open to criticism, particularly the continued attempts to stimulate the uterus with little or no rest period. The conditions that should be fulfilled before elective induction is undertaken are given as follows:

1. There be no cephalopelvic disproportion.
2. The fetus must be mature and should be presenting by vertex.
3. The head must be engaged.
4. The cervix should be soft, partially effaced, and at least 1 cm. dilated.

If the above mentioned conditions are fulfilled, most writers have found induction to be quite simple, employing stripping of the membranes or amniotomy, with the occasional use of Pitocin in ½ to 1 minim doses.[2,3,4]

The use of the catheter and pack as a means of induction of labor has been generally discarded because of its obvious infection and trauma dangers. Quinine also has largely lost its place in the induction of labor due to infant death and infant deafness reports in which some of the dosages were quite small.

Although all studies do not agree, this series confirms the general impression that an increase in maternal morbidity accompanies induction. Antibiotic therapy was not generally employed as prophylaxis in this series. However, 15 patients who did not reveal morbid temperature received penicillin in the forty-eight hours following delivery. In this group of 465 induced patients, there was an 8 per cent maternal morbidity compared to a 5.1 per cent figure for the entire group of 2,713 delivered in this two-year period.

There was a definite elevation in the incidence of postpartum hemorrhage; this group, 17.3 per cent of the total, accounted for 33 per cent of the hemorrhages occurring in the period under study. Nine of these hemorrhages were attributed to uterine atony.

Four of the premature infants delivered were in the so-called convenience group. This is a situation in which the physicians must accept the entire responsibility inasmuch as the dictum that the infant be mature prior to elective induction is an accepted one.

The neonatal mortality was slightly lower than the figure for the entire group delivering in this two-year period and it should be. The one infant in the convenience group expired of atelectasis which, of course, is a frequent concomitant of prematurity.

In closing, I would like to offer a quotation which I believe every physician should heed before taking upon himself the responsibility of an induction: "The primary indication must always be, is the patient better off with the uterus empty; or if the infant is alive and in good condition, is its chance of survival increased by early delivery."[1]

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Transient Cerebral Paralysis*

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THE SUBJECT of transient cerebral paralysis is a most controversial one. Basically, the controversy is this: Is transient cerebral paralysis due to vasospasm or to organic obstruction of one of the blood vessels of the brain?

The proponents of the former theory feel that a fleeting and localized vasospasm is the underlying cause, whereas the organic obstruction supporters insist that the initial step is an organic occlusion or stenosis of a cerebral vessel, that the prompt recovery is due to the collateral anastomotic vessels furnishing blood supply to the ischemic zone and that subsequent recurring symptoms result from fluctuations in the adequacy of the collateral blood supply.

I should like, first of all, to present the case report of a patient who demonstrates this particular problem.

CASE REPORT

A man, age 56, an insurance agent, had no previous history of illness and no history of head injury or convulsions. Blood pressure one year before was recorded at 142/100. In the four months prior to his present trouble, he had had occasional episodes of lightheadedness with visual blurring and epigastric distress usually lasting two to three minutes and relieved by belching.

While on a week-end trip in March 1952, he had just arisen and was shaving when the fingers of his right hand became numb and then his right leg and the right side of his face. A local physician examined him thirty minutes later. The paresthesia lasted about one hour, but slight paresis of the right arm with definite astereognosis persisted for about four hours. Blood pressure was 180/105. He had a slight nuchal headache, but neurologic examination was otherwise negative.

The remainder of that day and the following day he was entirely asymptomatic and was negative to neurologic examination. Roentgenograms of the skull and funduscopic examination were negative. The neurosurgical consultant felt that the patient had had a vasospastic episode and advised consideration of cervical sympathectomy at a later date if symptoms recurred frequently.

He returned to his home by train thirty-six hours later feeling perfectly well. He arrived home at 9:00 p.m. and retired soon after. He awakened at 2:00 a.m. with a severe nuchal headache, was aware of some numbness in both hands, difficulty in swallowing and in articulating clearly, and noted weakness of the left side of his face. The examining physician, who arrived in fifteen minutes, noted a blood pressure of 180/100, dysarthria, dysphagia, and left facial paresis. All of these symptoms cleared in about thirty minutes and soon after he was able to go back to sleep.

The next morning he was asymptomatic except for a mild nuchal headache, which resembled a tension headache. He was tense and understandably anxious. Blood pressure was 140/100 and neurologic examination was entirely negative. He was hospitalized for three weeks. Five weeks after his transient cerebral syndrome he was urged to begin to get back into his work. This he did not do to any degree for another three weeks. Particularly during the first eight weeks and to a progressively lesser degree since, he experienced continuing anxiety and with it a lack of confidence and initiative. Blood pressure varied between 120/80 and 160/100.

At the present time, six months later, he has had no more transient cerebral attacks and is carrying on his usual duties although exhibiting some personality change in the form of lack of initiative, self-confidence, and much anxiety. His eye grounds reveal arteriolar changes corresponding to a group I hypertension and at no time have shown evidence of increased intracranial pressure. His electrocardiogram is normal and no murmurs are to be heard in the heart.

The cerebral vasospasm theory was first proposed by Peabody[1] in 1891 to explain a case of a man of 56 with six transient attacks of hemiplegia. At necropsy, though the cerebral vessels showed gross atheromatous change, no infarct or arterial occlusion could be found. Since that time, vasospasm has been a popular means of explaining fleeting episodes of motor paralysis or sensory symptoms. Cerebral vasospasm was likened to the coronary spasm of angina pectoris and the arterial spasm in the leg which was the designated cause of intermittent claudication. As the syndromes of angina pectoris and intermittent claudication have come to be recognized as due to organic arterial occlusive disease, so have many eminent neurologists argued the existence of cerebral vasospasm.

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EXPERIMENTAL EVIDENCE FOR AND AGAINST CEREBRAL VASOSPASM

Anatomists have shown that the cerebral arteries have very thin vessel walls composed mostly of collagen and with very little muscle fiber.[2] Structurally speaking then, such vessels are not the type capable of vasospasm intense enough to produce cerebral ischemia.

The intracerebral vessels are not end vessels, as previously thought. Rather, anastomotic collateral channels for the blood supply of any given area of brain tissue do exist. This is an important consideration if one attempts to explain focal paralyses, lasting but a few minutes to a few hours, on the basis of actual organic occlusion of a vessel, for only by such collateral channels could an ischemic zone receive blood quickly enough for symptoms to disappear in a few minutes.[2]

Forbes,[3] in studying the physiology of the cerebral vessels, has shown that only very feeble vasoconstriction of the pial vessels, 7 per cent, occurs from stimulation of the cervical sympathetic as compared with intense vasoconstriction, 56 per cent, of skin vessels from identical stimulation. Adrenalin administered locally is a very feeble constrictor of pial vessels, while if given intravenously, actually dilates them. The most powerful vasodilators of cerebral vessels are metabolic[4] — increased CO_2 concentration and anoxemia — while papaverine, experimentally, is a very weak vasodilator.

However, it has been shown by Penfield[5] that pronounced vasospasm of the pial vessels can occur. He observed that when he induced focal convulsive seizures by electrical stimulation of certain foci in the brain, localized spasm of the pial vessels did occasionally appear after the seizure was over.

CLINICAL EVIDENCE FOR AND AGAINST CEREBRAL VASOSPASM

The most effective argument of the vasospasm adherents is that only vasospasm could account for the fleeting nature of the symptoms, an aphasia or hemiparesis which clears completely in minutes or hours.

Foster Kennedy[6] reports the case of a man of 40 with only mild hypertension who had 25 attacks of aphasia and right hemiplegia in four hours with no trouble thereafter. Another patient of his experienced 26 episodes of right hemiplegia in a single thirty-six-hour period and none in a three-year follow-up thereafter. Such case reports make the theory of vasospasm an attractive one.

Recovery from cerebral paralysis after administration of vasodilators has been offered in support of the vasospasm theory. A recent paper by Russek[7] describes a series of cases of transient recurring focal paralyses with dramatic results from papaverine. The reported success of stellate ganglion block in the treatment of cerebral embolism and thrombosis has been given as evidence that cerebral vasospasm does occur.[8] Indeed, some neurosurgeons who subscribe to the vasospasm theory are beginning to advise superior cervical sympathectomy in individuals having repeated transient paralyses.

Those who believe that these transient paralyses are due to organic occlusion or stenosis of a vessel point out: [2,9,10]

In the hypertensive group, no sharp line is drawn between the transient episodes of aphasia, weakness, and so forth, and the longer lasting and extensive paralyses in which complete recovery is not obtained — that is, both are frequently seen at different times in the same individual. Furthermore, well-detailed pathologic studies by various writers in cases of malignant hypertension reveal that multiple very tiny, often microscopic, infarcts are found to account for the focal and often transient symptoms present during life. Finally, the extreme narrowing of retinal arterioles, seen in hypertensive encephalopathy, which had been considered proof perfect of vasospasm, has been shown to be due to actual edema of the intima of the arteriole.

In cases of cerebral embolism, in the presence of mitral heart disease and auricular fibrillation, in which no one denies that an organic embolus actually occludes a cerebral vessel, focal weakness or paresthesias are frequently seen which clear entirely in a few minutes or a few hours. If a solid obstruction, such as an embolus, can produce symptoms which pass off in minutes or hours, then a thrombus should be able to produce equally transient symptoms.

It is that group of cases in which repeated transient paralyses recur in the presence of a normal blood pressure — or at most a mild essential hypertension — without evidence of coronary or rheumatic heart disease from which an embolus might arise and without significant peripheral arteriosclerosis, in which vasospasm formerly seemed the only explanation. However, in recent years, the syndromes of stenosis or occlusion of the basilar artery, its branches, or of the internal carotid artery with the production of transient motor and sensory symptoms have been described with increasing frequency.

BASILAR ARTERY OCCLUSION

Kubik and Adams,[11] in reviewing autopsies at Massachusetts General Hospital, found an incidence of basilar artery occlusion of 1 in 300 and studied in detail 18 such cases. Of greater importance to the subject of transient cerebral paralysis, they reported an additional 7 cases that survived with transient symptoms, which they felt were due to stenosis of the basilar artery or occlusion of one of its branches.

The pons receives its blood supply from the basilar artery while the midbrain is supplied by branches of the basilar and posterior cerebral arteries. The exact clinical picture in basilar artery occlusion is dependent on the segments of the pons or midbrain deprived of their blood supply by the occlusive process.

The principal symptoms and signs of basilar

TABLE I

BASILAR ARTERY OCCLUSION

Headache – Dizziness	Crossed paralysis
Initial confusion	Unilateral paresthesias
or coma, often clears	Bilateral Babinski –
Dysarthria	Quadriplegia
Dysphagia	Pupillary abnormalities

artery occlusion are enumerated (table 1). The patient often regains consciousness after an initial period of confusion or coma. Dysarthria and dysphagia are evident if the corticobulbar tracts are involved while the appearance of Babinskis, hemiplegia, or quadriplegia is dependent on extent of involvement of the corticospinal tracts in the pons. The appearance of a crossed paralysis, usually the third, sixth, or seventh cranial nerve on one side with weakness of a contralateral extremity, is characteristic of a lesion of the pons. There are several case reports in the literature of patients with basilar artery stenosis or occlusion exhibiting personality change, nervousness, and emotional instability.

If one subscribes to the theory of transient cerebral symptoms on the basis of organic occlusion of a vessel, our patient can be classified as a thrombosis of a pontine branch of the basilar artery on the basis of the unilateral paresthesias, seventh cranial nerve weakness on the left, right arm and leg weakness on the right along with dysphagia and dysarthria.

OCCLUSION OR STENOSIS OF INTERNAL CAROTID ARTERY

Traumatic thrombosis of the internal carotid artery with aphasia and right hemiplegia was first described by Verneuil in 1872.[12] Nontraumatic thrombosis was not recognized clinically until the advent of angiography. Ameli[12] has recently reviewed 33 such cases in the literature and added 6 of his own. All 6 of these were proved by angiography; none died. Some had only transient symptoms with complete recovery while others showed residual weakness in an extremity.

Table 2 lists the principal clinical features of internal carotid stenosis or occlusion. The most common site of obstruction is just above the bifurcation of the internal and external carotid, and the predominance of males is much greater here than in cerebral thrombosis elsewhere in the brain. Since the left internal carotid is more frequently involved than the right, the most characteristic clinical syndrome is one of transient aphasia with right hemiparesis. After several fleeting episodes of weakness, aphasia, or

TABLE II

CHRONIC OCCLUSION OR STENOSIS OF INTERNAL CAROTID ARTERY

Sex incidence: males predominate 7:1
Side: two and one-half times more common on left
Site: just beyond bifurcation most common
Peripheral vascular disease commonly associated
Condition remains stationary for years
Symptoms after fall in blood pressure:
Sleep, hemorrhage
Aphasia
Transient weakness, paresthesias
Astereognosis in two cases
Occasional visual blurring
Headache, coma or convulsions uncommon

paresthesias, the patient may remain well for years.

Denny-Brown[4] points out that while sudden and complete occlusion of either the basilar or internal carotid arteries may lead to early coma and death, in cases of slowly progressive stenosis, an episodic insufficiency of the circle of Willis results in recurring transient cerebral paralyses. A fall in systemic blood pressure which further compromises an already defective cerebral circulation may account for the recurrence of transient cerebral paralysis during sleep or after a massive gastrointestinal hemorrhage.

The clinical picture produced by the syndromes of organic occlusion or stenosis of the basilar or internal carotid artery is seen to be identical to many – if not all – the cases reported in the literature by other authors as being due to vasospasm.

SUMMARY

1. It must be said that there is still a wide divergence of opinion as to the mechanism behind the production of transient cerebral paralysis.

2. This is no longer of just theoretic interest for the proponents of the vasospasm theory, who number among them many neurosurgeons interested in this subject, advocate medical vasodilators – such as papaverine or nicotinic acid – or surgical intervention in the form of superior cervical sympathectomy. Such measures are considered useless, and at times even harmful by the organic obstruction group who cite instances of exacerbation of symptoms after a drop in systemic blood pressure.

3. The experimental and pathologic evidence seems weighted in favor of organic obstruction as the initiating factor.

4. The evidence that transient cerebral paralysis can result from proved organic obstruc-

tion to a cerebral vessel by thrombosis of the basilar or internal carotid arteries or by cerebral embolism is most impressive.

5. That vasospasm is never a cause of transient cerebral symptoms has not been disproved.

6. Only time and carefully controlled studies will answer the question of whether medical vasodilators or surgical sympathectomy deserve any role in the management of this group of cases.

7. With careful scrutiny of individual cases and with the use of newer diagnostic methods such as angiography, many, if not all, cases formerly classified as cerebral vasospasm may be found to be due to organic occlusive disease.

8. It is suggested — but not proved — that the symptoms of the patient, whose case report is presented in this paper, were due to thrombosis of a pontine branch of the basilar artery and not to cerebral vasospasm.

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Faulty cerebral hemodynamics is thought to cause the rare syndrome of fainting or vertigo, with or without convulsions, after paroxysms of coughing and is known as tussive syncope.

A form of symptomatic epilepsy is at least partly responsible, believes Desmond S. O'Doherty, M.D., of Georgetown University, Washington, D.C., who cites abnormal encephalograms in all of 5 recent cases affecting 4 elderly men and 1 woman. An additional factor is probably some form of cortical dysfunction.

The condition is usually associated with pulmonary emphysema and chronic bronchitis with cough. Pulmonary emphysema builds up intrathoracic pressure. The added stress of coughing impairs cardiac output and produces cerebral congestion and anoxia.

The affected group presumably also have hypersensitive vascular reflexes. The stimulus comes from vagal sensory end organs in the larynx or bronchi but may originate in the esophagus, so that syncope results from swallowing.

Desmond S. O'Doherty: Tussive syncope and its relation to epilepsy. Neurology 3:16-21, 1953.

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.*

Fulminating Meningococcemia with Bilateral Adrenal Hemorrhage

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THIS CASE is reported because less than 200 cases have been described in the literature, and because this is the first case to be recorded in this area, where two general hospitals have had 288,000 admissions since 1885.

Voelcker[2] first reported this disease complex now known as the Waterhouse-Friderichsen syndrome in 1894. In 1911 Waterhouse[3] presented an 8 months old child with this disease, and in 1918 Friderichsen[4] reported a similar case.

In the majority of cases the etiologic agent is the meningococcus. Most of the cases have occurred in children. The majority die within 24 hours of the onset and bilateral adrenal hemorrhage occurs in 95 per cent of the cases.[5] The adrenal glands undergo a series of morphologic changes associated with acute stress.[6] Superimposed upon these changes, in cases of meningococcal septicemia, are extensive hemorrhages so that the adrenal glands are unable to supply any of their hormone at a time when it is most needed. At autopsy the medulla and cortex cannot be differentiated on section, the picture being one of massive intracapsular hemorrhage. The cutaneous hemorrhages which occur are supposedly due to the Shwartzman phenomenon.[7] The adrenal lesions are considered to be a by-product of general toxemia, probably part of the alarm reaction, not necessarily a result of the Shwartzman mechanism.[8]

Fulminating meningococcemia with shock may simulate the Waterhouse-Friderichsen syndrome. In the former there are no adrenal hemorrhages. The adrenal hemorrhages and toxemia may be quantitative, and mild to moderate cases may occur that are fully compatible with recovery. Hodes[9] suggests that the circulating eosinophil count may be of value as a guide in the prognosis and treatment of meningococcal infections and that cortisone may prove to be of value in treatment.

Fig. 1. See text page 351.

CASE HISTORY

B.D. (No. 94692), a five year old white girl, became ill on February 5, 1952. Her face and arms rapidly became cyanotic, and she was admitted to the hospital at 9:00 a.m. on February 6. Her birth weight was 2 pounds and she had cerebral palsy. She had been hospitalized for bronchopneumonia in 1948. When first seen, she was in shock, her pulse was 200, and her blood pressure 60/10. Her skin was covered with ecchymoses, petechiae and cyanotic areas which did not fade on pressure. Eyes, ears, nose and throat were clear, no heart murmurs were heard, the lungs were clear and the liver, spleen and kidneys were not palpable. Reflexes were hyperactive.

Accessary clinical findings showed a temperature of 106.8°(R), weight 40 pounds, hemoglobin 88 per cent, and white count 22,000 with 90 per cent polys. The urine showed 6 to 8 white cells. The urine culture grew out a B. coli. Blood culture was sterile. Lumbar puncture was done and yielded yellowish, cloudy, cerebrospinal fluid, which contained 675 white cells per cubic millimeter. The cells were mostly PMN's. The spinal fluid sugar was decreased, and the protein was 349 mg. per cent. Direct smear of the cerebrospinal fluid showed gram negative intracellular meningococci. These same organisms were found in blood smears from the petechiae.

She was started on parenteral fluids and also given 200 cc. of blood. Penicillin was given intramuscularly, and terramycin[9] was given intravenously.

Two cc. of adrenal cortical extract were given every two hours intravenously. She was digitalized with 8 cc. of Digalen. At 5:30 p.m. her temperature was 105, and she was still in shock. She expired at 6:00 p.m. on February 6th.

Autopsy Report:

The body was that of a well developed, well nourished female child 4 years of age. Scattered petechiae were present over the arm, abdomen, thighs, legs, wrists and hands. Ecchymotic extravasations were present about the face, shoulders, and thighs. There was no generalized lymphadenopathy or icterus present. The chest and the abdomen were opened in the usual manner. The heart weighed 65 grams and was somewhat flabby in consistency. There was a small amount of fluid in the pericardial cavity. The aortic and the mitral valves appeared to be somewhat reddened and injected but no evidence of vegetations was present. The heart chambers were free of thrombi or emboli. There were no congenital abnormalities or defects. Both the parietal and visceral pericardium contained a few scattered petechial hemorrhages. The right lung weighed 260 grams and the left lung weighed 220 grams. The pleural cavities were free of fluid. The visceral pleura contained scattered petechial hemorrhages. The lungs were both heavy and congested and on section considerable oozing was present. The cut surface was deep red in color. There was mild hilar adenopathy but otherwise the mediastinum was clear. The liver weighed 650 grams and was rather flabby in consistency. It was of a deep reddish-brown color and on section appeared markedly congested. The spleen weighed 45 grams and was intensely congested. The pancreas appeared normal. Both adrenal glands were completely replaced by hemorrhage (see figure 1). No normal adrenal tissue was discernible, either from the medullary or the cortical areas. The gross appearance was simply that of a large blood clot capping the kidney having the general contour of an adrenal gland. The right kidney weighed 35 grams and the left kidney weighed 30 grams. Both kidneys were markedly congested. The pelvis, ureters, and bladder were clear. The retroperitoneal tissues were clear. The alimentary canal was without abnormality except for scattered petechiae in the serosal surface.

Histological examination of the myocardium showed a moderate interstitial edema. A cellular infiltrate was not present. However, examination of the lung showed the alveolar capillaries to be intensely congested. Many of the alveolar spaces were filled with red blood cells and hemosiderin-laden phagocytes. Some contained scattered PMN's, particularly about the peripheral areas of the space. The bronchomucosa was reddened but was otherwise clear. The pulmonary vascular tree was clear. The liver showed the sinusoids to be intensely congested.

Examination of the spleen showed the venous sinusoids of this organ to be packed with erythrocytes. The pancreas appeared to be normal. Examination of the adrenals showed no viable, normal parenchyma to remain. Both glands consisted of blood clot. A massive hemorrhagic necrosis had replaced all adrenal tissue bilaterally. The kidneys showed the glomeruli to be intensely congested. A few red blood cell casts were present in the collecting tubules. The proximal convoluted tubules showed marked cloudy swelling. The peritubular plexus was markedly congested.

Cause of death: Waterhouse-Friderichsen's syndrome secondary to meningococcic septicemia.

Anatomical diagnosis: Meningococcic septicemia; massive bilateral adrenal hemorrhage; toxic congestion of liver, spleen, kidneys, and lungs; generalized petechial hemorrhages.

SUMMARY

A case of the Waterhouse-Friderichsen syndrome was presented and the literature was briefly reviewed. The patient died less than 24 hours after the onset of the disease. At autopsy bilateral adrenal hemorrhage was found.

We are indebted to Dr. M. M. Heffron, Bismarck, North Dakota for his referral of this case.

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Histoplasmosis in North Dakota*

C. C. Smith, M.D.

Mandan, North Dakota

In February, 1952, four workmen, A.B., W.H.G., J.S.S. and W.A.C., who were engaged in wrecking an old building in Mandan, North Dakota, all became ill at about the same time. Their symptoms, which seemed to be common to all of them, were malaise, chills, fever, some cough and a general feeling of undue fatigue.

The building they were razing was of brick and wood construction and had stood vacant for a number of years. It had been used as a mattress factory during the depression years and at that time a number of people complained of feeling badly due, they thought, to the dust. Material for these mattresses had been shipped in from the South.

The four men were sick from a week to more than a month, and lost at least that amount of time in their regular work. They consulted a local physician who told them he thought it was influenza. Two seemed to be more ill than the others. One of them was admitted to a local hospital. Chest x-ray films were taken and from this and the other symptoms, tuberculosis was suspected. He was kept in isolation, later released when negative sputum examination and negative skin reactions were reported. No other diagnosis was made, however.

One patient who was still feeling badly went to the Northern Pacific Hospital at Glendive, Montana. There chest x-ray films were taken and blood sent to Communicable Disease Control Center, Atlanta, Georgia. Since there was such similarity of onset and symptoms in all four men and since they were all employees of the Northern Pacific Railway, the other three were called in and x-rayed and blood sent to the CDCC at Atlanta. All blood samples were reported as positive for histoplasmosis.

On July 15, 1952, J. Thomas Grayston, M.D., of the Kansas City Field Station, Epidemiological Services, visited Mandan investigating these cases, which had been reported by the Montana State Board of Health.

All four men were called in and interviewed in regard to their work, symptoms, etc. They all gave histories of working in this dust and all becoming ill at about the same time and with a similarity of symptoms. The wife of one of the men, W.H.G., had visited her husband while at work and she too had similar symptoms. All four were given skin tests for blastomycosis, coccidioidomycosis, tuberculosis, and histoplasmosis. Blood was also taken from all.

In 48 hours skin tests were read and reported as follows: all negative for other diseases except histoplasmosis. Results are shown in table I.

TABLE I

Patient	*Histoplasmosis*	*Complement Fixation*	*Precipitin*	*Histoplasmosis Result and CDC No.*	*Blastomycosis Result and CDC No.*	*Coccidioidomycosis Result and CDC No.*
A.B.	Erythema 2 cm.	4	64	H-1250 Positive 1:8	B-259 Positive 1:8	C-372 Negative
W.H.G.	Erythema 4 cm. Induration 1 cm.	4	16	H-1248 Positive 1:64	B-257 Negative	C-370 Negative
J.S.S.	Erythema 1½ cm.	4	0	H-1247 Positive 1:32	B-256 Positive 1:4	C-379 Negative
W.A.C.	Erythema 5 cm. Induration 2 cm.	8	16	H-1249 Positive 1:2048	B-258 Negative	C-371 Negative
Mrs. W.H.G.	Erythema 1 cm.	0	0			

Dr. Grayston, accompanied by one of the Custer District Unit personnel, collected earth samples from the vicinity of the wrecked building, also the old court house, old Fort Lincoln and other sites. Some anxiety was felt about the swimming pool being in such close proximity to the razed building.

The last x-ray films of these four patients showed increased calcifications of their lesions. They were all definitely improving.

C. C. Smith *is district health officer, Custer District Health Unit, Mandan, North Dakota.*

*From the office of Dr. Russell O. Saxvik, North Dakota State Health Officer, Bismarck, North Dakota.

Recognition should be given to Dr. M. A. Shillington, chief surgeon, Northern Pacific Railway Hospital at Glendive, Montana, for his alertness in recognizing the possibility of histoplasmosis, and to Dr. J. Thomas Grayston, epidemiologist, for his follow-up in these cases.

Transactions of the North Dakota State Medical Association

Sixty-Sixth Annual Meeting

Minot, North Dakota, May 9, 10, 11 and 12, 1953

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PROCEEDINGS OF THE HOUSE OF DELEGATES of the North Dakota State Medical Association Sixty-Sixth Annual Meeting First Session, Saturday, May 9, 1953

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. A. E. Spear, at 8:00 p.m. in the Skyline room of the Clarence Parker hotel, Minot, North Dakota, May 9, 1953.

Dr. E. M. Haugrud, chairman of the Credentials committee, reported that all credentials were in order and a quorum of 16 duly elected delegates were present. The Secretary, Dr. E. H. Boerth, called the roll. The following doctors responded.

G. W. Toomey, Devils Lake; W. R. Fox, alternate, Rugby; C. V. Bateman, Wahpeton; E. M. Haugrud, Fargo; Nelson Youngs, Grand Forks; C. M. Graham, Grand Forks; R. E. Mahowald, alternate, Grand Forks; J. D. Craven, Williston; A. R. Sorenson, Minot; D. J. Halliday, Kenmare; W. Gilsdorf, Valley City; R. O. Saxvik, Bismarck; R. B. Radl, Bismarck; R. W. Rodgers, Dickinson; Tom Pederson, Jamestown; and K. G. Vandergon, Portland.

Sixteen delegates answered the roll call. The Speaker declared a quorum present.

The Speaker next introduced Dr. Mayer, president-elect of the South Dakota State Medical association, who invited the North Dakota State Medical association to join them for a joint annual meeting in 1956, the occasion being the 75th anniversary of South Dakota organized medicine.

The matter of the invitation to meet with the South Dakota State Medical association was tabled until the meeting of the Second Session of the House of Delegates.

The motion was made and seconded that the minutes of the last meeting, as printed in THE JOURNAL-LANCET, be approved and adopted without the formality of being read.

Dr. E. H. Boerth, Secretary, presented the following report, as prepared for the Handbook, which was referred to the reference committee on reports of the president, secretary, and special committees.

SECRETARY'S REPORT

MEMBERSHIP: The total membership for 1952 was 384. Of this number 362 paid their annual dues and 10 were honorary members. Eight members died during the past year and several have left the state, either to practice elsewhere or to enter the military service. Twelve doctors are now in the service, making a total membership of 384. This total is the same as in 1951.

Table I shows the annual membership for the past eight years. From this table one can readily see that the membership dropped until a low of 313 paid members were recorded in 1945. Since that time, there has been a slow but appreciable gain in membership.

TABLE I

COMPARISON OF ANNUAL MEMBERSHIP

	1945	1946	1947	1948	1949	1950	1951	1952
Paid memberships	313	322	342	356	364	356	362	362
Honorary members.	9	9	8	5	13	12	11	10
Dues cancelled, military service	59	57	4	—	—	—	11	12
	379	335	350	361	377	368	384	384

Table II shows that the annual dues for 1953 are coming in quite promptly. There are still a number of members, however, who have not paid their 1953 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 II

	May 1 1947	May 1 1948	April 15 1949	April 30 1950	April 30 1951	April 15 1952	April 20 1953
Paid-up members	316	320	302	309	307	249	296
Honorary members	8	6	9	11	11	8	9
To be honorary			4	1	2	2	3
Dues cancelled, military service						11	12
Associate		1	1				
	324	327	316	321	320	270	320

STATE ASSOCIATION MEMBERSHIPS

	1952 Reg. & Rtd.	1952 Hon.		1953 Reg. & Rtd.	1953 Hon.	
First	61	—	—	67	1	—
Devils Lake	18	1	1	24	—	3
Grand Forks	—	—	2	48	—	—
Kotana	12	—	—	12	—	—
Northwest	38	—	1	24	—	2
Sheyenne Valley	8	1	—	10	1	—
Sixth	53	8	3	57	8	3
Southwestern	15	2	—	15	—	—
Stutsman	23	—	1	18	—	1
Traill-Steele	9	—	—	11	—	—
	237	12	8	286	10	9
	249			296		

A.M.A. GENERAL MEMBERSHIPS

	1952	1953
First	59	64
Devils Lake	18	24
Grand Forks	—	42
Kotana	11	12
Northwest	35	24
Sheyenne Valley	8	10
Sixth	47	57
Southwestern	—	11
Stutsman	22	—
Traill-Steele	7	9
	207	253

Several of the societies show a paid-up membership 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 is encouraging to note that the report shows a great many more paid-up members in 1953 than in 1952, at the time of this report.

The Secretary has tried to keep in touch with the operations of the state office. Mr. Limond and his staff have been doing an excellent job and it is recommended that they continue in office for the ensuing year.

E. H. BOERTH, M.D., Secretary

EXECUTIVE SECRETARY'S REPORT

LEGISLATION: Your Executive Secretary spent a most educational sixty-day period at the 33rd Legislative Assembly of North Dakota. Since I spent practically fifteen hours a day with our elected representatives, I believe I became rather well acquainted with a goodly portion of them. This fact should hold me in good stead for the session in 1955.

As you all know by now, oil legislation held the limelight, but the medical profession was interested in a few bills. The four-year medical school bill (S 184) was passed and has been signed by the Governor. Your President, O. W. Johnson, M.D., and H. M. Berg, M.D., chairman of your Committee on Medical Education, did fine work in trying to enlighten certain key legislators on the dangers of a time limit in setting up a four-year medical school by 1956. Various members of your Committee on Public Policy and Legislation were contacted and also aided in this program of enlightenment. Suffice it to say that the legislators did not "see the light" and Senate Bill 184 was passed. I hope to have the chance of giving a complete verbal account of my activities on this particular bill and others before the Council and the House of Delegates, since it would double the size of our Handbook to give a written account of our interest in bills dealing with health and education.

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, Berg, Kermott, Saxvik, and others, visited the Capitol and met with certain of the legislators plus appearing before committee hearings. Dr. O. W. Johnson did a fine piece of work in appearing before the senate Appropriations committee in support of Senate Bill 65 dealing with the "exceptional" child.

On the national scene, great interest by the medical profession as a group was found in President Eisenhower's Reorganization Plan No. 1, which elevates the Federal Security Agency to cabinet rank with the appointment of a practicing physician to the post of special assistant to the secretary, Mrs. Hobby. Also of interest to physicians is the Reed-Keogh bill, concerned with voluntary pension systems for the self-employed and professional people, which may have a hearing before the house Ways and Means committee before May 10 at which time the A.M.A.'s representatives are to be heard. Another piece of legislation which is of interest to medicine is the Bricker resolution to outlaw treaties and executive agreements which supersede the laws of the United States. The Bricker resolution is aimed at the International Labor Organization, which is definitely socialistic in my opinion.

It is suggested that there be some definite changes in our legislative committee structure. It is necessary that the North Dakota State Medical association have a closer individual contact with our state legislators in their home territory. Your executive secretary, therefore, suggests that a member of our association be selected, on the basis of interest in and knowledge of politics, for each of the forty-nine legislative districts. From these forty-nine physicians a potent core of ten or twelve be selected who will be the liaison men between your state office and the home fronts. It is extremely vital that personal contacts be built between the legislator and the doctor of medicine. This suggestion may seem very much like the ward technic in our large cities, but it is necessary if we wish to continue to give the people of North Dakota ever improving health and medical care irregardless of the whims and fancies of any North Dakota legislative assembly. The people and their elected representatives need enlightenment.

STATE OFFICE: There was no summer lull this past year at your state headquarters in the Little Building in Bismarck, according to your office secretary, Mrs. Margaret Fremming. She was kept busy on School Health lectures (where medicine and dentistry cooperated) at the five teachers colleges, on monthly newsletters, cancer seminars for lay leaders, interprofessional liaison committee for health meetings, on planning and carrying through on our first area medical-press-radio conference, and on many other plans and innovations for the giving of better service to the membership of the North Dakota State Medical association.

The work of the Veterans Medical Service division is to be found in its report in the Handbook.

MEETINGS: Your Executive Secretary attended many meetings and made several personal contacts with individual physicians, newspaper editors, legislators, radio station personnel, hospital administrators, nurses, dentists, pharmacists, and others. A complete listing will be found in the travel log of the executive secretary a little further on in these paragraphs.

Your President, Dr. O. W. Johnson, and your immediate past President, Dr. W. E. G. Lancaster, did a splendid job in handling the school health lectures previously mentioned.

It is felt that the various committees were not too active this year. There should be some thought given to further streamlining. Your state office has aided in the work of those committees which were active this past year. It is suggested that the meetings of the various committees be held in the early fall and through the early winter months. If this is done, it will facilitate getting out the Handbook by the middle of April, since the state office could call for final committee reports by March 15. Your reference committees of the House of Delegates would then have sufficient time to give serious consideration to the reports by the several committees before the annual meeting and thus expedite the functions of the House at your yearly convention.

FINANCE: The Treasurer's report continues to show a fairly respectable balance. But you will note the expenditures of the association exceeded the income by $2,930.70. Some serious and constructive thought needs to be given this situation. Your Executive Secretary feels sure that the Council will solve this problem since most of you are aware that a positive and forward-looking program of public relations needs money to function. And that it is in good times that we levy against ourselves substantially to protect against the future possibility of encountering bad times when the levies may need a reduction.

Your state office remained within its budget and it is our hope that the office always will.

The collection of dues continues to be slow in many instances. Your state office was in receipt of 1952 dues as late as November and December of 1952 when, according to the association's constitution and by-laws, all dues are to be in from the district societies on or before the first day of March in each year. All societies are urged to be prompt.

Your Executive Secretary also feels that a more strenuous effort to swell our membership rolls should be made at the local level. This coming summer, I hope to aid in this suggestion by contacting the secretaries of the district societies in regard to doctors of medicine residing in the society's territory whom your state office has record of not being members.

ANNUAL SESSION: Your Executive Secretary wishes to thank the members of the Northwest District Medical Society with whom he has worked in connection with the 1953 meeting. It should be noted that the annual meeting continues to operate with a deficit although there was not as large a deficit from the Fargo meeting of 1952 as in previous ones. Whether this will hold true for the present Minot meeting remains to be seen. Your state office is continuing its attempts to interest more commercial exhibitors again this year.

THE TRAVEL LOG: Just in case some of the members of the association have called this office in the past year and found me absent or may have had a tardy reply, the following will show, for the most part, why the above may have been the case.

1952–

May 16-17—Minot. Attended conference on school health education and met with representatives from the North Dakota State Medical association, state department of health, state teachers colleges and the medical center. Attended a dinner meeting of the officers of the North Dakota State Dental association.

May 26, 27, 28—Minneapolis. Attended the 99th annual meeting of the Minnesota State Medical association with Dr. W. E. G. Lancaster.

June 5-6—Bismarck. Attended a meeting on North Dakota Indian affairs with Dr. Shelby of Elbowoods and Dr. Van Sandt of Washington, D.C.

June 13-14—Fargo. Attended a planning on school health education lectures and also a meeting regarding quacks in the field of cancer.

June 22—Rugby. Met with President O. W. Johnson on committee appointments.

June 27—Grand Forks. Attended a planning with Dr. Smeby, president-elect of the North Dakota State Dental association, Dr. O. W. Johnson, Dean W. F. Potter, and Professor Arleigh Lincoln in regard to the July lecture tour on school health education.

June 28—Grand Forks. Attended meeting of advisory committee to the medical center.

July 9-10—Grand Forks. Attended meeting of the state board of medical examiners.

July 11—Langdon and Walhalla. Met with Mr. Ed. Franta, executive secretary of the North Dakota Press association in Langdon regarding the press-radio conference to be held on September 26th in Fargo. Went on to Walhalla and met the president of the North Dakota Press association, Mr. Everett Knudson and discussed plans for the conference.

July 12—Grand Forks. Attended final day of meeting of the state board of medical examiners. Called on Mr. Henry Dibbern, advertising manager of the Grand Forks Herald.

July 14—Fargo. Visited Blue Cross and Blue Shield offices.

July 21—Mayville and Grand Forks. School health lecture at the teachers college with Dr. W. E. G. Lancaster. Called on Dr. A. E. Culmer, Jr., secretary, Grand Forks District medical society, regarding participation in the press-radio conference.

July 22—Ellendale. School health lecture at teachers college with Dr. W. E. G. Lancaster. Visited the new hospital, newspaper office, Dr. Ellis Oster (new in town) and the druggist, Mr. Leiby.

July 23—Minot. School health lecture at the teachers college with Dr. O. W. Johnson. Visited with Mr. Harlan Black, president, North Dakota State Pharmaceutical association.

July 24—Dickinson. School health lecture at teachers college with Dr. O. W. Johnson. Visited the local newspaper.

July 25—Valley City. School health lecture at teachers college with Dr. W. E. G. Lancaster and lunch with members of the Sheyenne Valley District medical society. Visited the local newspaper.

July 26—Valley City. Committee meeting on review of past week's school health lecture tour. Representatives present were from the North Dakota State Medical association, North Dakota State Dental association, state teachers colleges, state department of health, College of Dentistry of the University of Minnesota, and the Medical Center of University of North Dakota. — Jamestown. Visited with Mr. Jeglum, executive secretary of the North Dakota Society for Crippled Children and Adults.

July 31—Fargo. Met with Dr. W. E. G. Lancaster regarding cancer seminars for lay leaders of the North Dakota Cancer society. Visited the Fargo Forum regarding the press-radio conference for September 26 in Fargo.

August 1—Valley City. Cancer seminar for lay leaders with Drs. Lancaster, Meredith, Gilsdorf, and Skelseth.

August 5—Grand Forks. Cancer seminar for lay leaders with Drs. Lancaster, Moore, Cardy, Fritzell, and Woutat.

August 8—Minot. Cancer seminar for lay leaders with Drs. O. W. Johnson, Lund, Breslich, Cameron, and Amstutz. Called on Mr. Ulric Gwynn, executive secretary of the chamber of commerce, regarding next state meeting of the North Dakota State Medical association.

August 15—Dickinson. Cancer seminar for lay leaders with Drs. Lund, Rodgers, Larson, and Berg. Visited with Dr. Gilsdorf, councillor, North Dakota State Medical association.

August 16—Dickinson. Called on Mr. DeForest, manager, Dickinson chamber of commerce, and Mr. Orville Burda, radio station KDIX.

August 20—Elgin. Met with Dr. M. S. Jacobson regarding participation of our committee on rural health at the North Dakota public health conference in Grand Forks on October 10 and 11. Discussed the survey of rural hospitals.

August 22—Crookston, Minnesota. Represented North Dakota State Medical association along with Dr. P. H. Woutat at the Northern Minnesota Medical Association meeting.

August 23—Fargo. Attended planning meeting on school health lectures for 1953. Representatives present from the North Dakota State Medical association, North Dakota State Dental association, University of Minnesota dental school, state department of health and the medical center, University of North Dakota.

August 26—St. Paul. Attended a preliminary meeting regarding participation at the president's commission on the health needs of the nation with Drs. Sorkness and Jacobson. States represented were North Dakota, Minnesota, South Dakota, Iowa, and Wisconsin.

September 2—Minneapolis. Attended meeting of President Truman's committee on the health needs of the nation with Dr. W. A. Wright, where the North Dakota State Medical association's stand was made known.

September 3-6—Chicago. Attended the successful PR Institute of the American Medical association with Dr. O. W. Johnson.

September 14—Jamestown. Attended the North Dakota Insurance Federation meeting.

September 17—Jamestown, Ellendale, and Edgeley. Visited the newspapers and doctors in these towns regarding the press-radio conference in Fargo, September 26.

September 18—Litchville, Valley City, LaMoure, and Oakes. Visited the newspapers and doctors in these towns regarding the press-radio conference in Fargo on September 26.

September 19—Fargo, Moorhead. Visited the Fargo Forum, Moorhead Daily News, and radio station WDAY, regarding the press-radio conference.

September 26—Fargo. Attended our first press-radio conference.

September 29—Bismarck. Attended the organizational meeting of the North Dakota Mental Health association.

October 9—Jamestown. Attended Jamestown Hospital medical staff meeting.

October 10-11—Grand Forks. Attended the North Dakota Public Health conference and participated as a panel member on the part of the program put on by our committee on rural health.

October 13-14—Grand Forks. Attended the cerebral palsy clinic. Attended the Grand Forks District medical society meeting. Spoke to the auxiliary to the Grand Forks District medical society.

October 21—Bismarck. Attended the meeting of the Sixth District medical society.

Octoher 23—Jamestown. Spoke at the meeting of the Stutsman County district medical meeting, along with Dr. O. W. Johnson.

October 24—Steele. Called on Dr. Zukowsky and the local newspaper editor.

October 27—Minot. Attended state conference on higher education. Met with Mr. Harlan Black, president, North Dakota State Pharmaceutical association; Mr. Arne Bjorke, president, North Dakota Hospital association; Miss Florence Sweeney, representing the North Dakota State Nurses association; Dean W. F. Potter of the medical school and our president, Dr. O. W. Johnson, to discuss mutual problems. Discussed the 1953 annual meeting plans with Dr. M. P. Conroy.

November 2—Bismarck. Attended medical economics committee meeting.

November 5—Rugby, Devils Lake. Visited at the Johnson Clinic and attended a medical-press meeting of the Devils Lake District medical society.

Novemher 6—Kensal, Jamestown. Called on Dr. Clarence Martin of Kensal on a matter for the state board of medical examiners plus Dr. Joseph Sorkness in Jamestown.

November 8-10—Omaha, Nebraska. Attended a regional A.M.A. legislative meeting with our president, Dr. O. W. Johnson.

November 15-16—Minneapolis. Attended the North Central Medical conference.

November 20-21—Minot. Attended the district society meeting with Dr. O. W. Johnson and also met with the committee on scientific program.

November 22-23—Fargo. Visited offices of Blue Cross and Blue Shield — also attended a meeting of the inter-professional liaison committee on health with Dr. O. W. Johnson.

December 1-5—Denver, Colorado. Attended the interim session of the A.M.A.

December 13—Fargo. Attended the meeting of the committee on crippled children.

December 15—Fargo. Attended a meeting of the First District medical society.

Decemher 30—Dickinson and Richardton. Met with Dr. Spear and drove him to Richardton to meet with the Sisters of the Richardton Memorial hospital.

1953—

January 7—Bismarck. Governor's health planning committee meeting.

January and February. Practically lived at the Capitol these two months except for the two following trips out-of-town in January.

January 9-10—Grand Forks. Attended the meetings of the state hoard of medical examiners and the advisory council to the medical center.

January 29-30—Minot.. Met with Drs. McCannel, Ayash, Sorenson, Conroy, and Mr. Brown of the YMCA regarding annual meeting plans.

March 19—Bismarck. Attended meeting of the committee on mental hygiene.

March 24—Minot and Kenmare. Traveled with Dr. M. S. Jacobson, chairman of the committee on rural health. Met with Dr. V. J. Fischer and Dr. Roger Sorenson regarding plans for the annual meeting. Surveyed the hospital facilities at Kenmare with Drs. Halliday and Gammell. Visited the newspaper.

March 25—Rugby and Leeds. Surveyed the Leeds Medical Center with Dr. Jacobson and visited with Dr. White. Attended rural health committee meeting in Rugby at the Johnson clinic.

April 2-3—Minot. Attended meeting of the Northwest District medical society. Discussed the final stages of annual meeting planning. Called on Mr. Harlan Black, president of the North Dakota State Pharmaceutical association and Mr. Ray Dobson of the Minot Daily News.

April 9-11—Bismarck. Attended the annual meeting of the North Dakota Press association.

April 11-12—Bismarck. Attended the meeting of the committee on medical economics.

April 14-15—Fergus Falls, Minnesota, and Fargo. Investigation trip.

April 16—Bismarck. Attended meeting of the North Dakota Tuberculosis and Health association.

April 17—Bismarck. Attended meeting of the committee on public health.

April 21-22—Dickinson. Attended the annual meeting of the North Dakota Hospital association.

April 22—Williston. Attended cancer seminar of the Kotana District medical society.

April 23—Minot. Attended cancer seminar of the Northwest District medical society.

April 27—Fargo. Attended cancer seminar of the First District medical society.

April 28—Valley City. Attended the cancer seminar of the Sheyenne Valley District medical society.
April 29—Jamestown. Attended cancer seminar of the Stutsman County District medical society.
April 30—Bismarck. Attended cancer seminar of the Sixth District medical society.
May 1—Dickinson. Attended cancer seminar of the Southwest District medical society.

THOUGHTS FOR THE FUTURE: Some of these thoughts or suggestions have been mentioned in the preceding paragraphs but will be listed here for the sake of condensation and convenience.

1. New legislative committee format for political action.
2. Separate committee dealing with public relations.
3. Medical-press-radio conferences to be held this fall with the legislators also invited.
4. Continuation of the rural health committee's small hospital survey.
5. Continuation of the Interprofessional Liaison Committee on Health. This committee is made up of representatives of the state associations of Dentistry, Medicine, Pharmacy, Hospitals, and Nursing.
6. Possible need for a constitutional change in the quorum requirements of the Council, which is now six. Since there are now but eight Councillor districts, the quorum required for doing business might be changed to a simple majority of the Council.
7. Each county of each district medical society should by now have a doctor as liaison officer with the county superintendent of schools. This plan was suggested last summer but was not carried through to a complete coverage of the state.
8. Each district medical society should have a doctor in each county in its territory as a liaison officer with the executive secretary of the county welfare board.
9. North Dakota to have a "General Practitioner of the Year." Our General Practitioner then could be entered in competition for the A.M.A.'s General Practitioner of the Year award.
10. It is possible that the House of Delegates might wish to give some thought to a change in selection and term of office of the members on the Committee for Scientific Program. The following is a plan that could be followed if changes were made in the association's constitution and by-laws:

    Committee on Scientific Program:

    President of the North Dakota State Medical association, general chairman; immediate Past President of the NDSMA, assistant to general chairman; Executive Secretary of the NDSMA, assistant to general chairman.
    Section on Medicine: A chairman and a secretary.
    Section on Specialties: A chairman and a secretary.
    Section on Surgery: A chairman and a secretary.
    Local Arrangements: A chairman.

    The term of office for each section would total six years since the secretary would hold his position for three years, then would move up to the chairmanship of his section for a three-year period. When the section secretary moved up to chairman, a new man would be selected as the secretary of the section. In this way, the city in which the annual meeting is to be held would always have an experienced member of the Committee on Scientific Program to aid in the planning if the appointments are made so the four annual meeting cities of Minot, Grand Forks, Bismarck, and Fargo have representation on the various sections. The incumbent president and immediate past president are on the committee to give aid and advice from their experiences of presiding at annual meetings. The local arrangements chairman has the job of running the meeting in his city plus any headaches that go with it. The executive secretary acts as a liaison between groups, arranges for the scientific and technical exhibitors to have space, and, in general, is the troubleshooter on this team.
11. Another suggestion is that the doctors of medicine on the medical school faculty at the University of North Dakota become fullfledged dues-paying members of the district and state societies. If this were so, these faculty members would have a vote in committee affairs on both the local and state level, thereby becoming integral parts of the North Dakota State Medical association.
12. Your state office is in receipt of requests from a few newspaper and radio people concerning a medical-press-radio code. It is suggested that the House of Delegates give some thought to this proposal.
13. Each district society to commence work on a historical sketch of its activities since receiving its charter from the North Dakota State Medical association. It is thought that as the years go by, the association may some day wish to publish a history of its activities plus historical sketches of its early leaders and members.
14. The House of Delegates, the Council, officers of the association, and individual members may wish to send congratulatory telegrams or letters to Mr. F. Manley Brist, legal counsel of the Minnesota State Medical association on completing twenty-five years of faithful service, and also to the officers of the Minnesota State Medical association at the time of their centennial meeting in St. Paul on May 18, 19 and 20, 1953.

ACKNOWLEDGMENTS: My sincere and heartfelt thanks to your president, Dr. O. W. Johnson, for the way he has so unstintingly and unselfishly given of his time and efforts to the duties of his office, to this association and its affairs, and to many groups of the general populace of North Dakota, I actually believe that he has been away from home more than he has been in Rugby with his busy practice. Dr. Johnson has traveled by plane, car, and train in this state and other states attending meetings and conferences on behalf of this association. My appreciation to Dr. Johnson and those other splendid gentlemen who have at all times been willing to help this writer in making this association function smoothly and positively in its program of the enlightenment of the public 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

Accounts of Executive Secretary

COMPARATIVE BALANCE SHEET
March 31, 1953

Assets	March 31, 1952	March 31, 1953
Cash in bank	$ 2,814.15	$ 3,840.44
	$ 2,814.15	$ 3,840.44
Liabilities		
Social security accrual	$ 51.52	$ 30.00
Withholding tax accrual	173.40	193.20
Fund Balances		
General fund	$ 1,387.77	$ 4,400.46
Convention fund	1,676.14	(72.86)
Medical examiner's fund	(47.87)	–0–
Public relations fund	(426.81)	(710.36)
	$ 2,814.15	$ 3,840.44

CONVENTION FUND
Receipts and Disbursements for the Period from April 1, 1952 through March 31, 1953

Receipts	$ 1,965.27	
Disbursements	3,714.27	
Excess of disbursements over receipts		$ 1,749.00
Less: Opening balance		1,676.14
Deficit in Fund, March 31, 1953		$ (72.86)

PUBLIC RELATIONS FUND

Receipts	$ 426.81	
Disbursements	710.36	
Excess of disbursements over receipts		$ 283.55
Add: Opening deficit		426.81
Deficit in Fund, March 31, 1953		$ (710.36)

MEDICAL EXAMINER'S FUND

Receipts	$ 47.87	
Disbursements	None	
Excess of receipts over disbursements		$ 47.87
Less: Opening deficit		(47.87)
Balance in Fund, March 31, 1953		None

GENERAL FUND
Receipts and Disbursements for the Period from April 1, 1952 through March 31, 1953

Receipts:		
North Dakota State Medical Assn	$14,870.00	
American Medical Association	78.00	
Auxiliary to No. Dak. State Med. Assn.	47.89	
Total Receipts		$14,995.89
Disbursements:		
Salaries	$ 7,901.21	
Office supplies and fixtures	650.02	
Telephone and telegraph	343.97	
Rent	390.00	
Cleaning	72.00	
Postage	133.71	
Travel	1,800.00	
Power and light	6.86	
Social security taxes	74.07	

Personal property taxes	16.01	
Donations, dues and subscriptions	110.00	
Repair and upkeep	6.25	
Auxiliary budget	200.00	
Audit	25.00	
Printing and miscellaneous	254.10	11,983.20
Excess of receipts over disbursements		$ 3,012.69
Add: Opening balance		1,387.77
Balance in Fund, March 31, 1953		$ 4,400.46

NORTH DAKOTA STATE MEDICAL ASSOCIATION
VETERANS MEDICAL SERVICE DIVISION
TRIAL BALANCE
March 31, 1953

	Debits	*Credits*
First National Bank	$1,867.08	
Medical accounts payable		$2,739.50
Veterans Administration Center	2,187.25	
North Dakota State Medical Association		2,500.00
Social security		12.66
Withholding tax		165.60
Salaries	275.00	
Postage	15.03	
Office supplies	1.46	
Rent	40.00	
Power and light	1.12	
Telepbone and telegraph	7.55	
Miscellaneous	10.00	
Bond	62.50	
Depreciation reserve		779.55
Furniture and fixtures	1,296.63	
Deficit	433.69	
	$6,197.31	$6,197.31

Report of the Treasurer

Dr. E. J. Larson, treasurer, presented his report as published in the Handbook:

TREASURER'S REPORT
May 9, 1952 to March 31, 1953
DR. E. J. LARSON, Treasurer

Receipts

Balance on hand, May 9, 1952, 1st James River National Bank		$26,333.59
Receipts from dues, May 9, 1952 to March 31, 1953	$14,870.00	
Interest on bonds	112.50	
Total Receipts		$41,316.09

Disbursements

Vouchers No. 214 to No. 235 inclusive.
Cbecks No. 617 to No. 638 inclusive.

5-13-52	
Fargo-Moorhead Orchestral Assn., state meeting	$ 200.00
Dean W. F. Potter, scholarship fund	500.00
Executive Secretary, State Med. Assn.,	
Woman's Auxiliary	200.00
Office expense	3,000.00
6-4-52 Mrs. R. B. Byrne, steno. expense	235.00
6-5-52 Globe-Gazette Printing Co., mimeo machine	550.00
6-21-52 N.W. Bell Telephone Co., tolls,	
Dr. O. W. Johnson	14.48
6-24-52 Dr. W. A. Wright, exp., A.M.A. meeting	196.11
7-16-52 Newberry Insurance Agency, treasurer's bond	25.00
7-21-52 Dr. O. W. Jobnson, telephone tolls	3.30
8-30-52 Office of Executive Secretary,	
Expense, public relations	426.81
Office expense	3,000.00
9-30-52 Office of Executive Secretary,	
Expense, annual meeting	890.27
Dr. W. A. Wrigbt, expense, Pres. Comm.	58.93
10-13-52 B.P.O. Elks Lodge No. 260, Fargo,	
Expense, medical press conference	417.89
10-28-52 Journal-Lancet, subscriptions	810.00
11-10-52 Dr. O. W. Johnson, telephone tolls	46.01
12-15-52 Conrad Publishing Co., insurance forms	265.20
12-22-52 Office of Executive Secretary,	
Office expense	3,000.00
12-30-52 Dr. W. A. Wright, delegate expense,	
A.M.A. meeting	229.25
12-30-52 Dr. R. B. Radl, expense,	
emergency medical service	96.55
3-25-53 Office of Executive Secretary,	
Balance, 1952-53 budget	3,635.00
3-31-52 1st James River National Bank, bank exchange	.90
Total Disbursements	$17,800.70

Total Receipts	$41,316.09	
Less Total Disbursements	17,800.70	
3-31-53 Balance on hand, 1st James River National Bank		$23,515.39
Bonds		4,500.00
3-31-53 Total Assets		$28,01.539

Dr. Spear, Speaker of the House, next introduced Dr. O. W. Johnson of Rugby, commenting on the remarkable job he had done during his year as president of the association. Dr. Johnson welcomed the members of the House of Delegates remarking that he had thoroughly enjoyed his work during the year and submitting the following report for approval.

The President's Report for the year 1952-53 is as follows:

Report of the President

May I take this opportunity to commend our new Executive Secretary for a job well done. I believe that we are getting welded into a closer knit association through his untiring efforts at organization. We did fail in some of the legislative efforts, and naturally there have been some criticisms, but I must also say that the profession as a group has not offered the support that we should have had in the last legislative session.

I personally feel that Mr. Limond has done an exceptional piece of work in the length of time that he has had to organize this association properly. Mr. Limond is the first full-time secretary that we have had, and needless to say is putting many things into order that we had not had properly functional heretofore.

I see a need for a "grass root" organization, "on the spot" members, for the purpose of contacting legislators personally. This could be done with little effort and be a very functional unit at the time of legislative sessions. This can be set up on a statewide basis by our legislative committee.

Some of the failure of committee meetings and other important meetings is the fact that members have to pay their own expenses. This is not a criticism, nor am I suggesting a change, but it is a matter for the house of delegates and council to consider. Part of the failure of committee is the lack of willingness on the part of members to foot their own bills for such meetings.

My recommendation would be to set up a Mileage and Per Diem Committee for your president. This is fast becoming more than just an honorary job. It is one requiring both time and expenditure in order to properly maintain our public relations program, and to take the active interest in inter-state medicine that the North Dakota Medical association should do in order to get our rightful recognition.

I have had the honor and privilege of attending meetings of most of the district societies. My effort at those meetings has been primarily for the purpose of attempting to make the individual societies cognizant of the fact that the state association, as such, is subservient to the many societies that make up our state unit.

I do not feel that we are utilizing our components to the fullest extent. One of the bodies within our society that is not as functional as it should be is the council. I am wondering if an executive body consisting of the state officers with the top officers of each society would be more functional.

I am deeply appreciative of the efforts so many have made in attempting to make this a successful year. The public relations of our society is still a problem, as was well shown at the last legislative session. Some of this might be because we, as medical practitioners, do not

fully use good public relations among ourselves.

There are some constitutional amendments that are necessary if the council is to be functional. The quorum will have to be revised from the present six to a lower number, as the number of societies in the state now total eight. Actually we have above six or seven functional units.

I would urge the Medical Education Committee to be well organized and to set their sights for the next two years, in order to be able to keep posted on changes which may take place in that field in our state.

Finally, I have attempted to represent the presidential office at meetings at the national as well as the local level. An itinerary in the Executive Secretary's report will indicate some of our travels.

O. W. JOHNSON, M.D., President

Report of the Chairman of the Council

Dr. R. H. Waldschmidt, chairman of the council, presented the following report which was referred to the reference committee on reports of the council, councillors, delegate to the A.M.A., and member of the medical center advisory council:

The council met May 10, 1952 in Parlor A, Gardner hotel, Fargo, North Dakota. Dr. A. D. McCannel, chairman of the council, called the meeting to order at 4:00 p.m. Roll call was taken and the following members were present: Drs. A. D. McCannel, A. R. Gilsdorf, J. F. Hanna, R. D. Nierling, R. H. Waldschmidt, C. J. Glaspel, C. J. Meredith.

Others present at the meeting were: Mr. L. A. Limond, Drs. W. E. G. Lancaster, E. H. Boerth, and E. M. Haugrud.

The council approved the purchase of a new electric mimeograph, after first having received a statement from Mr. Limond that a larger type machine would be profitable. He was able to obtain $100 on the old machine as a trade-in. The cost of the new machine was $550. This was moved by Dr. Waldschmidt, seconded by Dr. Meredith, and motion carried.

Dr. Lancaster appeared before the council with the request for a donation of $200 to help defray the expense of the Fargo-Moorhead Symphony Orchestra concert. Dr. Waldschmidt moved that this be approved; Dr. Gilsdorf seconded the motion, and the motion carried.

Drs. Gilsdorf, Nierling and Waldschmidt were appointed to the auditing committee.

Mr. Cohen of THE JOURNAL-LANCET was granted the privilege of the floor, and he informed the council of some very constructive changes that had been made in the type of articles appearing in THE JOURNAL-LANCET, and he stated that he hoped the council would see fit to renew the contract for another year. It was moved by Dr. Glaspel, seconded by Dr. Waldschmidt that the contract for THE JOURNAL-LANCET be renewed for a period of one year. Motion carried.

Dr. Lancaster spoke briefly on the need of improving our relations with the public. Mr. Limond continued the discussion and stated that it was his hope to bring about a better feeling between the newspapers and the medical profession. He expected to try out a plan which had been in operation in Minnesota and found to be very successful. In brief, it would consist of a meeting at some central point where the newspaper editors would be guests of the medical association. Panel discussions would be carried on, questions would be asked and answered relative to the medical needs of each community. It was suggested that Mr. Manley Brist, who has been the attorney for the Minnesota state board of medical examiners for many years, would be an excellent speaker on this occasion.

There being no further business, Dr. Waldschmidt moved, Dr. Gilsdorf seconded, and motion carried to adjourn.

May 11, 1952

The council met May 11, 1952 in the South room of the Gardner hotel, Fargo, North Dakota. Dr. A. D. McCannel, chairman of the council, called the meeting to order at 5:00 p.m. Roll call was taken and the following members were present: Drs. A. D. McCannel, A. R. Gilsdorf, J. F. Hanna, C. J. Glaspel, R. H. Waldschmidt, C. J. Meredith, R. D. Nierling.

Others present were: Dr. E. H. Boerth, Mr. L. A. Limond, Drs. J. Sorkness, E. J. Larson and W. E. G. Lancaster.

The first order of business was consideration of the budget. It was moved by Dr. Waldschmidt, seconded by Dr. Nierling, that the following budget be adopted:

North Central conference	$ 100.00
Official meeting, stenographer	175.00
JOURNAL-LANCET	800.00
Salary, executive secretary	5,200.00
Rental	360.00
Lights	25.00
Telephone	300.00
Office supplies and postage	800.00
Stenographer	2,700.00
Traveling expenses, executive secretary	2,400.00
Miscellaneous fund, executive secretary	750.00
Woman's Auxiliary	200.00
Scholarship	500.00
Committee, public policy and legislation	3,000.00
Total Budget	$17,310.00

This is approximately the amount which we receive from membership dues.

After considerable discussion relative to the student loan fund, it was decided that the matter be tabled for the present, until after a conference with Dean Potter relative to the necessity of such a fund.

Due to an oversight, Dean Potter had not been officially informed that the council had appropriated $500 at its meeting one year ago for scholarship prizes to be given in the medical school. The chairman of the council therefore dictated a letter to Dean Potter, telling him of such action, and verbally instructed Dr. Larson to forward him the check for that amount with the request that the Dean notify the council at his convenience the distribution and allocation of this money.

Dr. Waldschmidt moved that the sum of $500 be allotted for the purpose of creating prizes and scholarships, with the request that a report be submitted by Dean Potter as to the allocation of this fund. This was seconded by Dr. Nierling and motion carried.

After considerable discussion, it was moved, seconded, and carried that Mr. Limond be allowed 7½ cents per mile for travel for the fiscal year.

The council instructed Dr. Larson, the Treasurer, to invest the association funds in guaranteed securities at more than one per cent.

The next order of business was election of officers. Dr. R. H. Waldschmidt was elected chairman of the council; Dr. J. C. Fawcett was elected vice-chairman; and Dr. C. J. Glaspel, secretary. Drs. Waldschmidt, Nierling, and Gilsdorf were elected to the executive committee.

Meeting adjourned.

In accordance with Dr. Waldschmidt's request that a report be submitted by Dean Potter as to the allocation of the $500 scholarship prize fund appropriated for the

University of North Dakota, the following is the report received from the dean:

THE NORTH DAKOTA STATE MEDICAL ASSOCIATION PRIZES

This association offers five prizes, of the value of $100 each, to he awarded as follows:

1. One to the student attaining the highest average mark in all of the required courses in anatomy in the first year.
2. One to the student attaining the highest average mark in all the required courses in physiology and pharmacology in the first and second year.
3. One to the student attaining the highest mark in all of the required courses in bacteriology and parasitology in the first and second year.
4. One to the student attaining the highest average mark in the required courses in pathology in the second year.
5. One to the student attaining the highest average in the work of the first year.

For the academic year 1951-1952 these prizes were awarded as follows:

Anatomy ..... Walter Harrison Moran, Jr.
Physiology and Pharmacology.. John Bentley Lunseth
Bacteriology and Parasitology.. John Bentley Lunseth
Pathology ..... Warren Robert Jensen
First Year in Medicine.. Walter Harrison Moran, Jr.

These prizes were presented at a special convocation held in the Student Union Building on August 19, 1952. At that same event, pictures were taken showing the presentation of awards by Dr. R. D. Campbell and Dr. R. E. Leigh, as well as the presentation of the check by the Woman's Auxiliary to the Student Loan Fund. Dr. O. W. Johnson presented the North Dakota State Medical association awards to the students.

R. H. WALDSCHMIDT, M.D.,
Chairman of the Council

REPORTS OF COUNCILLORS

First District

This district society had an unusual year in that for three meetings we were hosts for the various groups. In April we met under the auspices of the North Dakota Cancer society for an informative discussion. The May meeting was represented by our own state meeting. Flood conditions caused some inconveniences which were difficult to take in stride. Then, in September we held the first meeting in this state between the press and the medical men in the eastern third of North Dakota. This forum was considered a success and should serve as an index of procedure for future meetings of this type.

Other meetings entertained speakers of note, including Drs. E. T. Bell, Malcolm Hargreave, A. V. Stoesser, Alex Barno, and Arnold Kremin.

Two of our dermatologists, Drs. Macaulay and Melton provided plans and technic which aided the Health department in smotbering an outbreak of ringworm of the scalp.

We elected these new men to membership: Drs. Wilbur Koons, Marshall Landa, A. G. Skjelset, D. W. Nagle, and D. T. Lindsay.

Death claimed Drs. P. H. Burton, pioneer physician and surgeon; J. F. Hanna, former state president; and J. H. Fjelde.

New officers for 1953 are as follows: President, Dr. A. C. Burt; vice-president, Dr. Frank A. DeCesare; secretary-treasurer, Dr. R. D. Weible.

The delegates to the state meeting are Drs. Bateman, Fortney and Haugrud.

W. E. G. LANCASTER, M.D.,
Appointee for Dr. Hanna

Second District

The Devils Lake District had ten regularly scheduled meetings over the past twelve months. Of these, we had outside speakers for the scientific programs at six meetings, scientific papers presented by the members of this district at three meetings, and a press-medical conference at one meeting. The meetings as a whole have been well attended, and interest has been very good. We have certainly had in our favor the fact that the last two winters have been relatively mild and the roads open. For the most part, harmony prevails among the membership.

Officers elected for the coming year are as follows: President, Dr. C. A. Corbett; vice-president, Dr. I. L. Lazarek; secretary-treasurer, Dr. L. F. Pine; censor, Dr. D. W. Palmer; delegate, Dr. G. W. Toomey; alternate delegate, Dr. William Fox.

One of our outstanding programs of the year was the press-medical conference on the local level. We had three newspapermen form this district in attendance, Mr. M. R. Graham of the Devils Lake Journal being the speaker for the press. At a subsequent meeting, this society went on record as favoring adoption of a plan patterned after the plan now in use in South Dakota for medical-press relationship. The society also went on record as wishing to urge the North Dakota State Medical association to consider, and if possible, adopt this plan or a modification thereof as a state-wide program.

JOHN C. FAWCETT, Councillor

Third District

The Third District is composed of the Grand Forks District medical society and the Traille-Steele medical society.

The Grand Forks District medical society has had seven meetings during the year, all of which were well attended. The September meeting, usually held in Grafton, was cancelled in order to permit members to attend the first medical-press meeting held in the state, at Fargo, late in September. The Grand Forks society was well represented at this meeting, which was inaugurated for the purpose of improving our relationship with the press of the state and discussing some of our common problems.

The October meeting was devoted to a discussion of cerebral palsy by Dr. Harry Barnett of New York. At the November meeting, Dr. T. Q. Benson of Grand Forks discussed aortic stenosis. At the December meeting, Dr. William Nelson of Grand Forks presented a paper on the early detection of cancer. At the January meeting the guest speaker was Dr. E. T. Bell of the Pathology Department of the University of Minnesota. At the February meeting, the president of the state society, Dr. O. W. Johnson of Rugby was our guest and he spoke of our past history and our future responsibilities. He also briefly commented on the various proposed measures before our state legislature, which are of interest to the medical profession. At the March meeting, Dr. Paul Bilka of Minneapolis spoke on modern concepts and diagnosis of rheumatic disease. The April meeting was held at the University in collaboration with the North Dakota Cancer society.

The officers for 1953 are as follows: President, Dr. Kenneth Fritzell, Grand Forks; vice-president, Dr. A. E. Culmer, Jr., Grand Forks; secretary-treasurer, Dr. Robert Painter, Grand Forks. Delegates to the state medical convention are: Dr. Nelson Youngs, Dr. C. M. Graham and Dr. W. A. Dailey, all of Grand Forks. Alternates are: Dr. R. E. Mahowald and Dr. V. S. Quale, Grand Forks.

The society has a paid-up membership of 60 and 55 of these have voluntarily paid their A.M.A. assessments. There are 37 members in Grand Forks and 23 from the adjacent areas.

The Traille-Steele District medical society at a regular meeting held in Mayville, October 22, 1952, elected the following officers: President, Dr. K. G. Vandergon, Portland; vice-president, Dr. Robert McLean, Hillsboro; secretary-treasurer, Dr. Syver Vinje, Hillsboro; delegate to state meeting, Dr. K. G. Vandergon, Portland; alternate delegate, Dr. William Buckingbam, Hillsboro; censor for three years, Dr. H. A. LaFleur, Mayville.

There were 12 members who paid state association dues, and 10 who paid A.M.A dues for 1952. There were 3 new members added during the year, and 1, Dr. Cable, who left to locate in South Carolina. To the date of this report, March 14th, we have 10 members who have paid state association dues and 8 the A.M.A. dues. There are 2 doctors in the district who are not members, but of these, 1 has sent in his application for membership.

During the year there were three regular meetings with good attendance. Our meetings are partly social and partly professional, since we have a Ladies' Auxiliary organization. The professional part is taken over partly by home talent and partly by. guest speakers. Thus at one meeting, Dr. Ralph E. Leigh, Grand Forks, gave a comprehensive address on the medical history in North Dakota during the past 25 years, and a full account of the two-year medical course at the North Dakota University. At another meeting, Dr. Little of Mayville, a member, gave an interesting and comprehensive address on the symptoms and treatment of gout.

At a later meeting, Dr. Christoferson of Fargo was introduced and spoke briefly to the members and an extended report was given by Drs. Vandergon and McLean on the medical-press conference held in Fargo on September 26, 1952.

C. J. GLASPEL, Councillor

Fourth District

We have two medical societies in the Fourth District, the Northwest medical society and the Kotana society, with headquarters at Williston.

We have had tbe following dinner meetings in the Northwest District medical society:

January 31, 1952—Trinity hospital. Election of officers. February 27—Clarence Parker hotel—Dr. F. D. Naegeli, Minot: "Vesical Neck Obstruction." April 3—St. Joseph's Nurses' Home—Dr. Lee Christopherson, Fargo: "Management of Acute Head Injuries." April 24—Country Club—Drs. Hagedorn and Donoghue of Mayo Clinic on "Carcinoma of Lung"—sponsored by the North Dakota Cancer society.

September 25—Country Club—Dr. Lloyd Sherman, Minneapolis: "Common Problems of Urology." Discussion of medical insurance problems by representatives of Souris Valley Life Underwriters' association. October 23—Country Club—Dr. Fred Z. Havens, Mayo Clinic: "Plastic Repair of Cleft Lip and Palate." November 20—Country Club—Convention planning with Dr. W. E. G. Lancaster, Fargo; Dr. C. H. Peters, Bismarck; Dr. O. W. Johnson, Rugby, and Lyle Limond.

The Fourth District has now a membership of 59. Ten new members have been taken in this year. Five have resigned from the society, 3 leaving the state, and 2 leaving for military service. During the year we had 12 meetings, held in Minot. They have all been well attended and very good programs have been extended on each occasion. The officers during the past year have been: President, Dr. Martin P. Conroy; vice-president, Dr. A. F. Hammargren, Harvey; secretary-treasurer, Dr. W. G. Ensign. Election of officers for 1953 was held at our regular meeting in January and the new president is Dr. Paul Breslich; vice-president, Dr. Henry Kernott; sceretary-treasurer, Dr. Olive Pitkin. Dr. Sorenson and Dr. Halliday were elected delegates to the state society, with Dr. Fritz Erenfeld as alternate. We had no deaths in our membership in the past year and our present membership is 59.

Our society is looking forward with a great deal of pleasure to entertaining the state medical meeting this year and have made every effort to cooperate with the state committee and build a program, and we hope that everyone will avail themselves of this splendid meeting and have a good time.

The Kotana medical society with headquarters at Williston had their election of officers. The new president is Dr. C. O. McPhail of Croshy; vice-president, Dr. P. O. C. Johnson of Watford City; secretary-treasurer, Dr. D. E. Skjei, Williston. They have a total membership of 12. One charter member, Dr. I. S. AhPlanalp, was lost hy death during the past year. Three meetings were held during the year and were very well attended.

A. D. McCannel, M.D., Councillor

Fifth District

The following is the councillor's report for the Fifth District for the year 1952.

Five meetings were held in our society during the year. The outstanding scientific meeting was that held under the sponsorship of the North Dakota Cancer society, at which Drs. Ylvisaker and Kinsella gave excellent papers on carcinoma of the stomach and tumors of the lung. Both talks were well illustrated with Kodachrome transparencies and x-ray slides.

Our society gained one new member, Dr. C. J. Klein, who located in Valley City. Our society now has 9 members, 8 practicing in Valley City. We lost one member in the person of Dr. Paul Cook who moved to California.

Officers elected to serve in 1953 are as follnws: President, C. Christianson; vice-president, C. J. Klein; secretary-treasurer, C. J. Meredith; delegate, W. H. Gilsdorf; alternate, G. Christianson.

C. J. Meredith, Councillor

Sixth District

Five meetings nf the Sixth District medical society have been held during the past year with an average attendance of 36. The membership nf the society is 73.

The present officers are: President, Dr. Edmund Vinge, Beulah; vice-president, Dr. Ernest Salomone, Elgin; secretary-treasurer, Dr. C. H. Peters, Bismarck.

New members added during the year were: Drs. Harold Kuplis, Turtle Lake; Franz Gutowski, Wishek; Philip O. Dahl, Bismarck; Johan A. Eriksen, Bismarck; Hugh R. Davidson, Riverdale; Zoya Kudinoff, Halliday; James J. Moses, Bismarck.

Dr. C. Heinzeroth, Turtle Lake, passed away during the past year.

Cuest speakers during the past year were: Dr. L. W. Larson, trustee of the American Medical association and a member of the Sixth District medical society, who spoke nn the "National Medical Problem." Dr. R. S. Ylvisaker, internist at Minneapnlis, Minnesota, who spoke on "Cancer of the Stnmach." Dr. J. T. Kinsella of Minneapolis who spoke on "Lung Tumors and Lung Disease." Dr. J. A. Myers, schnnl nf public health, Minneapolis, whn spoke on "The Physician and Tuberculosis." Dr. Harvey Nelson, chief surgeon of the Soo Line Railroad, Minneapolis, who spoke on "Treatment of Fractures." Dr. W. F. Potter, dean of the University of North Dakota Medical School at Crand Forks who spoke on "The North Dakota Medical School." Dr. Joseph Sorkness of Jamestown, who spoke on "Some Prohlems of the Prostate Cland."

R. H. Waldschmidt, M.D., Councillor

Seventh District

The Stutsman County medical society, which is the Seventh District society, had fnur meetings during the year 1952.

On January 31, 1952, a dinner meeting was held. Melvin Coons, chief of laboratories of the state health department at Crand Forks, gave a talk and shnwed slides of lahoratory examinations and discussed facilities available to the profession from the state health department. He also explained the blood bank. A film on curare was shown. Follnwing officers were elected: President, Dr. R. S. Woodward, Jamestown; vice-president, Dr. B. Maloney, LaMoure; secretary-treasurer, Dr. R. D. Nierling, Jamestown; delegate, Dr. T. E. Pederson, Jamestown; alternate delegate, Dr. Philip C. Arzt, Jamestown.

A special meeting was held on April 16, 1952. Mr. Lyle Limond, executive secretary of the state medical association, made a few remarks and a plea for attendance to the state convention in Fargo, May 10-13. Dr. Lund explained the cancer program sponsored by the state cancer society. Dr. Ylvisaker of the University of Minnesota spoke on the subject of early detection of carcinoma of the stomach, and Dr. Kinsella, also of the University of Minnesota, followed with a discussion of lung tmors illustrated hy numerous x-rays and pathological specimens.

The next regular meeting was held on Octoher 23, 1952. Speaker for this meeting was Dr. O. W. Johnson, president of the state medical association. He spoke on the present needs of the state, including health education program for schools, the A.M.A. foundation for aid to medical schools, membership in the world medical association, and increase in the number of nurses and nursing schools.

The last meeting was held on Novemher 20. Dr. Kosalka, chief medical officer of the Veterans hospital at Fargo, presented a talk and slides on hepatitis.

The society has had one meeting thus far in 1953. On January 22 a dinner meeting was held. The following officers were elected: President, Dr. R. E. Lucy, Jamestown; vice-president, Dr. Clarence Martin, Kensal; secretary-treasurer, Dr. John Jansonius, Jamestown; delegate, Dr. T. E. Pederson, Jamestown; alternate delegate, Dr. John Elsworth, Jamestown.

A committee was appointed to study the welfare rates for the state of North Dakota.

R. D. Nierling, Councillor

Ninth District

The Southwest District medical society had four official meetings in the year 1952, all at Dickinson.

The first regular meeting was held March 20. The purpose of this meeting was to appoint corporation members to the Blue Cross and Blue Shield and to take up any active district business. Dr. R. W. Rodgers and Dr. Ralph J. Dukart were appointed as corporation members of the Blue Cross and Blue Shield.

The second meeting was held Octoher 18 at the Hotel Ray. Cuest speaker for the evening was Dr. Sidney K. Shapiro, psychiatrist, of Minneapolis, whose topic was "New Concepts of Epilepsy and Their Diagnosis and Treatment." Routine business meeting was held at this time.

The third meeting was held on December 6 and was again a dinner meeting at the Hotel Ray. A very fine scientific program was presented. Cuest speakers were Dr. A. V. Stoesser of the department of pediatrics, University of Minnesota, who spoke on "Differential Diagnosis and Treatment of Respiratory Diseases in Children." Dr. Norman Nelson of the department of internal medicine, University of Minnesota, then spoke on the subject of "Psychosomatic Medicine." This was a large meeting and we had many guests from districts outside of our own, including three visitors from Montana. Routine business meeting was also held.

The last meeting of the year was held December 27, for the purpose of business only. Officers for 1953 were elected: President, Dr. Harlan Larson; vice-president, Dr. Julian Tosky; secretary-treasurer, Dr. H. L. Reichert; delegate to the state meeting, Dr. R. W. Rodgers; alternate delegate, Dr. H. E. Culoien; councillors to the society, Drs. C. A. Bush, A. Martens, and R. L. Coulding.

Special discussion was held regarding welfare board rates in this area. An economic committee was appointed consisting of Dr. R. W. Rodgers, as chairman, and Drs. H. L. Reichert and A. R. Gilsdorf to investigate and attempt to work out a proper fee schedule.

Dr. A. J. Spanjers of our society is now serving in the armed forces. Dr. Rohert F. Cilliland transferred from Carrington, Tri-State District medical society, to the Dickinson clinic, Dickinson. Dr. Gilliland had spent the previous two years on active duty with the North Dakota National Guard.

A. R. Cilsdorf, M.D., Councillor

REPORTS OF COMMITTEES

The reading of the following reports was dispensed with and the reports referred to the proper reference committees:

Committee on Official Publication

The committee on official publication, composed of Drs. L. W. Larson, W. H. Long, C. W. Toomey and the undersigned, beg leave to report that in their opinion The Journal-Lancet is doing a good joh of reporting the actions of the house of delegates and other activities of the association.

They note a marked improvement in the scientific material presentcd. No complaints or suggestions have been received.

P. C. Arzt, M.D., Chairman

Committee on Crippled Children

I wish to submit a report of the activities of the committee on crippled children for the current year.

A meeting was held on Saturday, December 13, 1952, at the Gardner hotel in Fargo. The members attending the meeting in addition to myself were: Dr. H. J. Fortin, Dr. J. C. Swanson, Dr. B. A. Mazur, Dr. A. E. Culmer, Dr. Joseph Sorkness and Dr. Robert Tudor. Mr. Lyle Limond attended the meeting in his capacity as executive secretary of the state medical association. Other physicians attending the meeting, not members of the committee, were Dr. Douglas T. Lindsay, Dr. George Foster, Dr. C. W. Hogan, and Dr. Paul Johnson. Dr. Johnson attended in his capacity as medical advisor of the crippled children's program. The other non-member physicians attended because of their interest in the changes in the rate schedule. Mr. Harold Hagen, director of the division of child welfare and Miss Margaret Lister, assistant to the director of crippled children's services of the division of child welfare also attended the meeting.

The meeting was called for the main purpose of adjusting the fee schedule of the crippled children's program. The present fee schedule was instituted during the depression years and is far out of line with present fees. The entire schedule was gone over carefully and recommendations made for increased fees for many items of professional care, laboratory work and x-ray studies. 1 am glad to report that this suggested revision of the fee schedule has since been approved by the public welfare board.

Eligibility for participation in the crippled children's program was also discussed. It was decided that there should be provisional acceptance for men to participate in the program who have completed their formal requirements of training in a specialty, who lack sufficient time in actual practice to take the board examinations; it was therefore recommended that physicians in this category be given a provisional status for from two to three years while obtaining their board approval. The committee accepted the following physicians to participate in the program on this basis:

Orthopedic surgery—Dr. Douglas T. Lindsay, Fargo; Dr. Ralph Vinje, Bismarck; and Dr. David Horner, Minot. Dr. Lee Christoferson was given the same status in neurosurgery.

The committee also accepted the following physicians to participate in the program either with board qualifications or eligible for their board approval: *Orthopedic surgery*—Dr. John D. Folsom, Grand Forks; Dr. Clifford W. Hogan, Jamestown; Dr. Paul Johnson, Bismarck. *Ophthalmology*—Dr. Burton Olson, Minot; Dr. John J. Ayash, Minot. *Otolaryngology*—Dr. M. Zwerling, Bismarck. *Pediatrics*—Dr. Olive Pitkin, Minot.

It was decided hy the committee that cases under the crippled children's program will not be referred out of the state for diagnosis or treatment without the recommendation of a specialist approved for practice under the program. Whenever possible, such referrals are to be in the field of the referring specialist's practice. If no such specialist is available, referrals should be made through a specialist in a related field or by a pediatrician. This matter was brought up because of some cases in which patients have been referred out of the state for conditions which it would be possible to treat in Nortb Dakota.

This covers the main points of the meeting.

L. G. Pray, M.D., Chairman

Committee on Necrology and Medical History
(1953)

As time proceeds it measures new events and the old slowly becomes dimmed to memory. Only occasionally has longevity extended the true pioneer doctor's life and practice to 1953. The very sturdiness of our pioneer men of medicine has built a strong foundation for our present practice. Several of the doctors in this report began their practice at or before the turn of the century. Let us not forget what they have done, not only for tbeir patients but also for their communities and the practice of medicine in North Dakota. Theirs is a noble example. It is not surprising that the editor of the Bismarck Tribune was moved to editorialize on these doctors of medicine incident to the death of a "country doctor."

PAUL H. BURTON, M.D.

Dr. Paul H. Burton died November 4, 1952. He was born in Boscobel, Wisconsin, July 16, 1876. Dr. Burton had the distinction of wearing one of the buttons presented by the North Dakota State Medical association indicating his having practiced medicine 50 years. His M.D. degree was awarded by the University of Minnesota about 1901. After this education, he interned as prison physician at the state penitentiary at Stillwater, Minnesota. Among his patients were such notorious cbaracters as Frank James, the brother of Jesse James, and Cole Younger, both members of the James gang. These two found their way into the Minnesota prison via the famous bank robbery at Northfield, Minnesota. It will be remembered that Dr. Wbeeler, a former Grand Forks physician, played an important roll in this episode, having shot and killed one of the robbers from his office window across the street from the bank.

While still attending the University of Minnesota Medical school, Dr. Burton spent some time at Kenmare, North Dakota. He understood tbe Old West and his face always lit up when telling of his experiences there where he made many long rides on horseback to attend some suffering rancher.

After graduation he practiced some time in Hallock and Red Lake Falls, Minnesota, before coming to Fargo where he went into the practice of medicine and surgery up to 1925. In 1925, he joined the formation of the Dakota Clinic. In this group he practiced up to the time of his death.

His civic activities were testimony to his interest in all the affairs of the community in which he lived. He served as a member of the Fargo school hoard, was on the county welfare board, and was instrumental in instigating the Five Year Child Welfare program which was financed by the Commonwealth Foundation. It is out of this program that some of Fargo's present-day welfare work originated.

He was one of the founders of the Fargo Rotary club and also a member of the Masonic bodies, Elks, and Fargo Country club.

Dr. Burton was active in medical society affairs. He was president of the Cass County society and president of the North Dakota State Medical association in 1932. He served on the state board of medical examiners. During World War 1 he headed the medical division of our Cass county draft board and in World War 11 was on the state appeal board. Dr. Burton was doing postgraduate work in Europe when World War 1 broke out. He was an early member of the American College of Surgeons.

Paul Burton has been characterized as a "rugged individualist." Certainly he was known for his blunt uncompromising attitude where a matter of principle was involved. But those who knew him well discovered he always had a helping hand and a sympathetic heart for those in trouble or difficulty.

Dr. Burton's first wife was Agnes Scott, daughter of the late Mr. and Mrs. W. A. Scott. To them were born two children: William, who presently heads the Windsor-Detroit Tunnel operation and resides in Detroit, Michigan, and Dorothy, who is Mrs. George Fisher and resides at Cheney, Washington. These children were young when Mrs. Burton died and on August 11, 1912, Dr. Burton married Hazel Hodgson, the daughter of the late Mr. and Mrs. P. A. Hodgson of near Gardner, North Dakota. Mrs. Burton is a graduate of St. Luke's school of nursing. They had two children, Dr. John Paul of Hattiesburg, Mississippi, and James Miner of Moses Lake, Washington.

And so another of the few Horseback and Horse and Buggy doctors still practicing has left us. Dr. Burton was never sick in hed until a pneumonia kept him down about a week one year ago. He often said, "There is no tragedy so bad as that of living to be too old." His death was sudden and unexpected. He died on election day. He had voted, and at noon went home apparently to take a short nap. He was found lying on his couch shortly after this. Certain it is, he did not live to be "too old."

J. E. COUNTRYMAN, M.D.

Dr. J. E. Countryman died February 15, 1953, in Wheeler, Oregon. He was born in Tweed, Ontario, in 1870. He graduated from Queen's University, Faculty of Medicine, Kingston, Ontario, in 1893. He was licensed to practice medicine in North Dakota in 1892. His first residence was in Drayton, North Dakota. While in Drayton, he was instrumental in organizing Fidelity Lodge, A. F. and A.M. and in Grafton was a member of Crescent Lodge No. 11 and St. Omer Commandery and Kem Temple of the Shrine at Grand Forks. Dr. Countryman practiced in Grafton from 1900 to 1938, at which time he moved to Arch Cape, Oregon, where he has made his home since that time.

Dr. Countryman served as a medical officer in World War 1. He is survived by a son, Dr. G. L. Countryman, at Grafton; three daughters, and a sister who resides in Kingston, Ontario.

Dr. Countryman is well remembered by the residents in and ahout his section of North Dakota. His practice goes back, bridging the pioneer days with modern medicine and practice.

Dr. Countryman served as president of the North Dakota State Medical association in 1910, and was a member of the state board of medical examiners for six years.

JACOB H. FJELDE, M.D.

Dr. Jacob H. Fjelde died Octoher 19, 1952, at the age of 54. He was born July 5, 1898, at Abercromhie, North Dakota, the son of a pioneer North Dakota physician, Dr. Herman O. Fjelde. The elder Dr. Fjelde was a leader in Norwegian-American cultural relations in the Northwest and was largely instrumental in the erection of statues of famous Norsemen in the community. He was responsible for placing five statues in Fargo-Moorhead. Among these were the statues of Rollo, famed Viking who founded Rouen, France, in the year 911, the statue of Wergeland, tbe poet, to be seen in Island park, also the stone from the home of Bjornson at the North Dakota agricultural college.

Dr. Fjelde attended the Abercrombie schools and later when his family moved to Fargo, the schools there and the North Dakota agricultural college and North Dakota university, completing his medical course at Washington university, St. Louis, where his medical degree was conferred in 1925. He returned there for postgraduate work and became a specialist in obstetrics and gynecology.

Returning to Fargo in 1927 he became affiliated with the Dakota Clinic until 1933 when he established an office in the Black building in Fargo. He was a member of the staff of St. John's and St. Luke's hospitals.

Shortly after starting practice, Dr. Fjelde did some early experimental work with the intravenous use of barbiturates in anesthesia. He had seen some work along this line at Washington University medical school and realized its possibilities when for the time they laid aside the work. His experiments together with other contemporary work proved the safety and wide use of this group of drugs.

When World War 1 began he volunteered for service in the U. S. Navy. He served as a noncommissioned officer in the medical corps. He was assigned to the Olympia, which had been Admiral Dewey's flagship, and for a time was in port at Murmansk and Venice. He saw the surrender of the German fleet at Scapa Flow.

On February 8, 1936 he married Norma Almos of Ambrose, North Dakota, daughter of Mr. and Mrs. Andrew Almos. Norma was a graduate of St. John's school of nursing and had been operating a private hospital at Ambrose.

In 1950, Dr. Fjelde was elected president of the North Dakota Physicians Service, operator of the "Blue Shield" physician, medical and surgical service. He continued active in this organization and was North Dakota's delegate to the annual meeting of the National Blue Shield in Biloxi, Mississippi, in 1951.

In 1942 he was elected president of the North Dakota Society of Obstetrics and Gynecology. He was a fellow of the American Medical association, a diplomate of the American Board of Obstetrics and Gynecology, and a member of the Phi Chi and Theta Chi fraternities, Fargo Assembly, Fourth Degree, Knights of Columbus, and the American Legion.

Dr. Fjelde was an avid hunter and lover of the out-of-doors. He spent his later summers at a cabin he built on Oak Island in the Lake of the Woods. His final illness incapacitated him for work in July 1951 and in spite of a brave fight, he died of heart and arterial changes.

He leaves Mrs. Fjelde, two daughters, Marcia, 13 and Andrea, 11, and a foster son, Bruce, by a previous marriage, who is in the Air Force. There also is a brother, Professor Olaf S. Fjelde, who teaches architecture at the University of Illinois, at Urbana, and two sisters, Mrs. C. B. Wright of Fargo and Mrs. P. C. Pratt of Gardner, North Dakota.

JAMES FRANCIS HANNA, M.D.

Dr. James Francis Hanna died October 14, 1952 at the age of 66. He was born in Page, Dakota Territory, October 4, 1886, three years before the Territory became a state. He was the son of Mr. and Mrs. James F. Hanna, who had homesteaded at Page in 1883. His father died in 1887. Dr. Hanna was graduated from Duluth Central high school aud in 1913 from the school of medicine, Marquette university, Milwaukee, Wisconsin.

As a boy and young man, he worked at many jobs—in the stock room of a wholesale drug firm, a shoe salesman in Milwaukee, and on railroad and telephone jobs. He received his license to practice medicine in North Dakota on January 8, 1915 and resided and practiced there up to the time of his death.

During World War 1, he served 23 months in the army medical corps. After his return to Fargo, he became associated with the McGregor, Hanna and Clay Clinic—later Hanna, Clay and Lancaster Clinic. When this group was dissolved in 1943, he joined the staff of the Dakota Clinic.

Dr. Hanna did postgradnate work at Tulane university, New Orleans; Cook County hospital, Chicago; Barnes hospital, St. Louis; and Leland Stanford university, Palo Alto, California. His internship was served in Milwaukee County hospital and Chicago Lying-in hospital.

His interest and training inclined his practice to obstetrics to which he very largely limited his practice. His influence in no small way contributed to the high standard of North Dakota obstetrics and the enviable record of vital statistics effected hy that field of medicine in our state.

Dr. Hanna was a member of St. Anthony of Padua Catholic church, and Alpha Kappa Kappa medical fraternity. He had served as president of the North Dakota State Medical association and president and secretary of the Cass County medical society.

He was also a diplomate of the American board of obstetrics and Gynecology and a member of other professional societies; Fargo Council, Knights of Columbus, and The American Legion. He was an officer in the medical corps, U. S. Army, during World War 1.

Few obstetricians attain the distinction of successfully delivering quadruplets with all four surviving. Dr. Hanna achieved this rare distinction in the case of the Brown quadruplets of Leonard, North Dakota (three boys and a girl). It is possihly the earliest diagnosis of quads ever made. An x-ray made early in pregnancy was properly diagnosed, indicating four babies. Fortified with this knowledge, he was able to carry the pregnancy to a successful conclusion in spite of many difficulties, especially in the later weeks of the pregnancy.

He married Mildred Elizabeth Reilly, April 27, 1918. Miss Reilly was a graduate of St. John's hospital training school of Fargo. Besides Mrs. Hanna, he leaves two sons, Paul Shelley Hanna, Grand Forks; and James Marshall Hanna, at home; and two grandchildren.

GEORGE EMERSON HEINZEROTH, M.D.

Dr. George Emerson Heinzeroth died November 6, 1952. He was born November 5, 1874 at Ashton, Illinois, the son of Mr. and Mrs. Michael Heinzeroth. He graduated from Ashton high school and from Loyola university in Chicago, where he received his M.D. degree in 1906. He was also a graduate of S. S. Still school of osteopathy, Des Moines, Iowa.

He came to Turtle Lake, North Dakota, in 1907, where he practiced throughout the rest of his life.

On May 28, 1907, he married Bertha Zillmer in Chicago, Illinois. He attended the Lutheran church, and was a member of the Masonic lodge, and El Zagal Shrine in Fargo. He served as a member of the Turtle Lake school board from 1924 to 1945, many years of that period as president of the school board. He was also mayor of Turtle Lake.

In addition to Mrs. Heinzeroth, he leaves one son, Dale, Fargo; a brother, Gust, Langdon; a sister, Mrs. Robert Moore, Polo, Illinois; and two grandchildren.

The following was an editorial published in the Bismarck Tribune at the time of Dr. Heinzeroth's death:

"He was not a selfish man. He did not ask much for himself, nor did he desire fame. He was not a vain man. He was humble in manner and inconspicuous in dress. In a crowd, he was quiet and unassuming. When he was needed, he was always ready.

"Once he drove ten miles over a snow-banked highway in an automobile and then seven miles over drifted country roads by team and sled to a little farm house where a small boy was lying at death's door. Once? Maybe a dozen times, maybe a hundred times. To get him, someone had gone on horseback to the nearest telephone. That was all it took. The hour of the day or night didn't matter. A child, a mother in pain needed him, and he was ready.

"How many times he answered those calls, how many times he brought hope and comfort, and sometimes life to stricken people not even he himself knew. He kept no count. Often he got no reward, other than that which tear-brimmed eyes and his own heart could give him. When he died, it was not as a rich man. He was still serving, and very happy in the knowledge that in his lifetime he had always helped as best he knew how and often at personal risk and sacrifice, those who called upon him for help.

"He was Dr. George E. Heinzeroth, for 45 years a doctor at Turtle Lake. When his funeral services were held here Sunday, the people who attended included many whom he had helped, many who felt that they had lost a great and true friend.

"But this tribute is not to Dr. Heinzeroth alone. It is to all the 'country doctors' who have gotten out of warm beds on nights when the prairie is swept by blizzard to ride or drive to a home where someone lay ill. Theirs has been a selfless service. Pioneers themselves, they have served the pioneers, and great should be the affection for them.

"We write not in memory of Dr. Heinzeroth, particularly—a humble, little known man who probably would have been most surprised that he should be the subject of such comment. But we are thinking also of those others in other small towns of North Dakota, men who came here as young men and have now grown old, who have known what it means to ride a huckboard behind a pair of ponies to deliver a baby, or remove an appendix, or amputate a limb in a lamp-lighted farm house, marooned in a sea of snow.

"Strong, courageous, dedicated, they have been giants on our prairies. May they find in this a small indication of the love and esteem in which the rest of us whom they have served hold them."

ELIZABETH P. RINDLAUB, M.D.

Dr. Elizabeth P. Rindlaub died August 5, 1952. Dr. Rindlaub was a native of Wisconsin and was born in Platteville where she began her education in the local schools. She graduated from a Wisconsin teachers college in 1893. After teaching two years she entered the University of Michigan medical school, receiving her medical degree in 1899. She came immediately to Fargo and joined her brother, Dr. John Rindlaub. A few years later they were joined by another brother, Dr. Martin Rindlaub. This formed a family group practice in the specialties of eye, ear, nose and throat diseases. Among the very earliest specialists in these fields in this state, they did much to furnish North Dakota with high grade specialist care. A number of young physicians joined this group and rounded off their training under their guidance. The success of these doctors speaks well for their experience with the Rindlaubs.

Dr. Elizabeth was the last survivor of this family group of doctors. Drs. Martin and John preceded her in death. For many

years they practiced in the deLendrecie building in Fargo and later were associated with the Fargo Clinic. This group helped set a high standard for specialists in our community.

Dr. Elizabeth was a member of the First Congregational church, Daughters of the American Revolution, Daughters of the American Colonies, the College of Surgeons, the National Academy of Ophthalmology and Otolaryngology, Gamma Phi Beta Sorority, and an honorary member of the Fargo Woman's club.

She is survived by two sisters, Mrs. John D. Wooledge of Fargo and Mrs. John H. Robertson of Platteville, Wisconsin.

GEORGE R. WALDRON, M.D.

Dr. George R. Waldron died November 25, 1952 at the age of 53. He grew up in North Dakota where his father practiced medicine. His medical degree was obtained in 1927 when he graduated from Northwestern University school of medicine. His internship was at Charity hospital, New Orleans, Louisiana. Dr. Waldron began his practice in Drayton, North Dakota, and in 1929 moved to Pembina where he practiced up to 1937 when he moved his practice to Cavalier, North Dakota. He was active in practice up to the time of his sudden death.

He was active in Masonic bodies and the Shrine at Grand Forks. He was chief rabban of Kem temple. Dr. and Mrs. Waldron, the former Mildred Chively, were married in Chicago June 26, 1926. Besides his wife, he is survived by two children: Charles, attending the University of North Dakota, and Frances, dietetics student in Minneapolis.

MILO H. CULBERT, M.D.

Dr. Milo Herman Culbert, Medina, North Dakota, died March 12, 1953 at Trinity hospital, Jamestown.

Dr. Culbert was born at Portland, Indiana, September 1885. He was a graduate of Portland high school, attended the University of Chicago and graduated from Northwestern medical school in 1910. He interned at St. Margaret's hospital, Hammond, Indiana, and was on the Chicago city board of health for many years. He came to North Dakota for his health in 1914 and was assistant superintendent of the state hospital. In 1916 he went to Tower City and later to Billings, Montana, returning in 1941 to Medina, where he has remained ever since.

Dr. Culbert was a charter member of South Gate Lodge No. 968, A.F. and A.M., in Chicago. Miss Voletta Cors and Dr. Culbert were married at Leeds, on July 18, 1916.

He is survived by his wife and two daughters, Mrs. Clarence Rudy, Jamestown and Mrs. James H. Sehon, Fort Worth, Texas; also two grandsons.

FRANK I. DARROW, M.D., Chairman

Public Health

A meeting of the committee on public health, state medical association, was held on Friday, April 17, 1953, in the office of the state health officer. The following were in attendance: Dr. R. O. Saxvik, chairman, Bismarck; Dr. C. O. McPhail, Crosby; Dr. A. F. Hammargren, Harvey; Dr. George Loeb, San Haven; Lyle Limond, executive secretary, state medical association, Bismarck; James Fenelon, state representative, National Foundation for Infantile Paralysis, Fargo; Kenneth Mosser, director of preventable diseases, state health department, Bismarck.

The 1952 report of the committee on public health was read by the chairman.

TUBERCULOSIS

The public health committee considered the present trends of tuberculosis in North Dakota. Particularly noteworthy was the reduction of tuberculosis cases reported from 292 in 1950 to 206* in 1952 and a decrease in deaths from 71 in 1950 to 45* in 1952. The committee expressed the continued desirability of intense case-finding with the mobile x-ray units and the need of continued effort to reduce the tuberculosis incident in the Indian population.

It is recommended that the state medical association notify the bureau of Indian affairs to intensify its case-finding practices on the several Indian reservations.

Further, it is recommended that the B.I.A. establish a distinct and purposeful health education program on the Indian reservations so as to more adequately acquaint the Indians with the need of tuberculosis control, management, and rehabilitation.

GAMMA GLOBULIN

The State Health council of the North Dakota State Department of Health in special session on April 9, 1953, requested that the public health committee of the state medical association consider the distribution of gamma globulin. After discussion, the committee advised that the distribution of gamma globulin be guided by the recommendations of the health resources advisory committee of the office of defense mobilization and approved the following with the request that this be distributed by the health department to all physicians in the state.

POLIOMYELITIS IMMUNE GLOBULIN SERUM

A. *Issuing of poliomyelitis immune globulin.*

The office of defense mobilization announced the controlling of gamma globulin and propose to allocate the total supply by methods which will offer the best effect from the amount available. Each state will receive about May 1, a basic allocation of globulin for use in protection from poliomyelitis.

1. It is requested each morbidity report card indicate on the line assigned to disease whether the case reported is "paralytic" or "nonparalytic."
2. A special form may be used by the physician to request immune globulin for the household contacts under 30 years of age. This form requires the patient's name and address and the name and age of each household contact. From this information, the allocation to the physician will be made based on the age of the contacts.
3. The dosage used is relatively large, 0.14 cc. per pound of body weight. Since weight and age are closely related the following procedure will be used in allocation of the poliomyelitis immune globulin.

Age	*Amount*
Under 6 months	2.0 cc.
6 months through 2 years	3.0 cc.
3 years through 15 years	1.0 cc. per year of age
16 through 30 and pregnant women	20.0 cc.

Since the vials contain 10 cc. each, the amount issued will be the least number of vials to total the required amount on the physician's request.

B. *Record of distribution required.*

Policies set at the national level require that accurate records be kept of the distribution of all poliomyelitis immune globulin used for the prophylaxis of poliomyelitis. The forms used by the North Dakota State Department of Health follow recommendations made by the office of defense mobilization.

GAMMA GLOBULIN FOR MEASLES AND INFECTIOUS HEPATITIS

The amount allocated to the state will be based on the average annual number of measles cases reported in the five-year period 1947-1951. Since measles, and particularly infectious hepatitis, have probably been under-reported, close rationing will be necessary even in this program.

Physician will be supplied upon request by letter or wire to the state health department. Physicians are urgently requested to restrict the use of gamma globulin to those susceptible individuals exposed to measles who have valid medical indications for prevention or modification, and to household contacts of infectious hepatitis.

"*Physician's Request for Poliomyelitis Immune Globulin*
For Household Contacts of Case of Poliomyelitis
(30 years and under, and pregnant women)

. . . . . .
Distribution Station
Patient . . . . . Age . . . .
Paralytic . . . . . Nonparalytic . . . . . .
Address . . . . . Date of Onset . . . . . .
Name of Household Contacts: Age
. . . . . .
. . . . . .
. . . . . .
. . . . . .

Estimate amount to issue from following table:

Age	*Amount*	Amount Issued
Under 6 months	2.0 cc.	. . . . .
6 months thru 2 years	3.0 cc.	
3 years thru 15 years	1.0 cc. per year	Lot No.
Pregnant Women	20.0 cc.	. . . . .

Physician . . . . . .
Address . . . . . Date of Request . . . . . .
This form must be forwarded to the Division of Preventable Diseases in order to obtain a replacement of the gamma globulin issued." PD-4/15/53

VENEREAL DISEASE

The committee considered certain public health aspects of the control of venereal disease and take this opportunity to notify the members of the association that: (1) the hospital bed program will be discontinued July 1, 1953; and (2) that penicillin in aqueous form in disposable syringes will be furnished without charge upon request of the physician treating a venereal disease on an out-patient basis. All professional fees for treatment will be the responsibility of the patient. The committee recommends a single dose million unit injection of penicillin for the treatment of acute gonorrhea.

RUSSELL O. SAXVIK, M.D., Chairman

Committee on Medical Education

(Report up to June 1952)

The meeting of the committee on medical education of the North Dakota State Medical association was held at the Gardner hotel on May 11, 1952, at 9:30 a.m. The following members of the committee were present: Drs. Berg, Tompkins, MacDonald, Meredith, Rodgers, Fortney, Wright, and E. J. Larson. Mr. A. F. Arnason, Dr. Archie McCannel, Dr. Jacobson, Dr. Saxvik, Dr. Lancaster, and Dr. O. W. Johnson were also present, as well as the following members of the University medical school faculty:

*Provisional

Harold Brody, Carl Calman, J. D. Cardy, W. E. Cornatzer, J. C. Davison, R. G. Fischer, H. E. French, A. R. Gault, C. J. Hamre, W. R. Koons, R. M. Marwin, P. H. Potter, W. F. Potter, E. B. Ruth, and Y. Tsumagari. Dr. McCannel gave the following report:

"The board of higher education has found it necessary to pay good salaries in order to obtain adequately trained men for the staff of the medical school. This has been done. The arrangements have also been made to provide opportunity for research. Through various grants, $180,000 is available at the present time for research studies."

Mr. Arnason gave the following report (which is to be treated confidentially).

"The oegotiations are under way with aoother medical school in a nearby state for traosferring the students for the last two years to that iostitution. These negotiations are in a talking stage and cannot be made public at this time." ○○

Dean Potter gave the following report:

"Only two of the present sophomore class have not been transferred to other schools for their last two years. Last year at this time there were ten that had not been transferred. The accreditation of the medical school has made the placing of these men easier than formerly. Dean Potter brought out the fact that under the preseot rules it is difficult to obtain permission for two members of the school of medicine to atteod the same meeting. He felt that this rule should be changed so that a larger number of the men from the school could attend the national meetings. He felt that this would be an added incentive in obtaining any addition to the staff of the medical school. He brought out that we could be accredited and could not meet the requirements for becoming accredited if we should add the third and fourth years to the medical school at this time. He felt that legislation forcing the addition of the third and fourth year immediately would result in our losing accreditation for the first two years. And we could not, under any circumstances, set up a four-year school which would be accredited under present cooditions. He stated that the University of Vermont has been for many years on the verge of losiog its standing as an accredited four-year school. However, they now have enough charity cases in two hospitals to provide the clinical material for the junior year. The cities from which these charity cases originate pay for the care of these patients and the medical school provides for their medical and surgical care. This would be impossible in North Dakota. The requirements io order to be accredited for a four-year school are that eight beds must be available for junior students. If we have forty students in the junior class this would require 320 beds for the junior class alone, to say nothiog of the other classes."

Dr. Lancaster gave the following report:

He stressed the need for more health education from the medical profession. He stated that the dentists are ahead of us in this regard. He felt that a health education program should be established in the teachers colleges and he would like to see this program originate from the medical school.

Dr. McCannel gave the followiog additional report:

He stated that a plan of making an arrangement with the University of Minnesota for the last two years was not origioal and that 13 states in the South are using this plan.

Dr. Hamre reported that the number of applications for admission to the medical school were considerably less than in previous years. The applicants were also much younger.

Many members of the committee made remarks in regard to the excellent work which had heen done previously by Dr. Ralph E. Leigh of Grand Forks on this committee. It was felt that a letter should be sent to Dr. Leigh from this committee commending him on his fine work. The chairman of the committee was iostructed to send such a letter, which will be done.

In general discussion it was brought out that the legislature would meet this coming year and that some arrangement should he made at the present time to see the proper education prograoi was arranged for and the proper committees were set up to haodle legislative problems. It was decided to submit the following two resolutions to the house of delegates. This was done. A letter from Dr. Stucke to the committee was read. Meeting adjourned.

H. M. Berg, M.D., Chairman

RESOLUTIONS

The committee on medical education wishes to submit the following resolutions:

I.

Whereas: There is a real need to have our North Dakota youths more adequately iostructed in matters of health by well informed teachers; and

Whereas: The presidents of the state teachers colleges have signified their desire to have such courses in health education conducted this summer in their regular summer school sessions; and

Whereas: This type of education can be jointly developed with the North Dakota State Dental association;

Therefore, be it resolved: That this health educational program be inaugurated under the directioo of the dean of the medical school and under the auspices of the medical center with the assistance of the state health department and the doctors of the state.

II.

Whereas: The North Dakota legislative assembly will meet io session this January 1953, and will undoubtedly discuss health matters; and

Whereas: Certain legislative health probleins are already in evidence;

Now, be it resolved: That this association establish a liaison with other ioterested groups and organizations to assist the legislature in promoting legislation which will be in the best interest for the health of the people of North Dakota.

(Report June 1952 up to May 1953)

House Bill No. 184 was passed during the last session of the legislature. As you all know, this bill makes it mandatory to have a three-year school in 1955 and a four-year school in 1956. A very active educational campaign was carried on in the legislature by Mr. Limond with some assistance from me, to give the legislature the facts in regard to this bill. Throughout the discussion with the members of the legislature on this bill, we stressed that the medical profession is not opposed to the bill but we did not feel that a four-year school would be advisable or feasible at this time.

At the time this bill was up for a hearing before the senate committee, as far as I know, no one else was preseot except the members of the committee theoselves. The hearing of this bill was very cleverly arranged so it was impossible for anyone to be present. The bill came up in the senate shortly after this hearing, before there was any opportunity to do any work in the senate opposing the bill.

The bill was supported by the Farmers Union, the Non-Partisan League, the Grand Forks chamber of commerce, by Mr. Bridston, Dr. Stucke, Mr. Day, and Mr. Streibel. It was impossible to prevent the passage of this bill through the house with so many groups supportiog the bill.

After this bill was passed in the senate, I received word through a Grand Forks doctor that Dean Potter was very much concerned about the bill and hoped that something could be done to prevent its passage in the house. I was informed that he did not feel that it was feasible in aoy way and that we should do everything we could here to defeat the bill io the house.

Mr. Limond and I, with material supplied by Dean Potter and obtained elsewbere, undertook to contact as many of the members of the house as possible and give them the facts in regard to a four-year medical school. We stressed the cost of the four-year medical schools in nearby states for the last two years and also stressed the fact that a 320-bed hospital had to be available for the junior class if there were to be 40 students io the class. We also stressed to all members that the medical profession did not oppose haviog a four-year school in the state.

At the hearing in the house committee, we were given ample opportunity to present our side of the case. It was arranged to have Dean Potter there. Dean Potter arrived on Sunday and the hearing was the following morning. Mr. Limond and I both contacted Dean Potter Sunday afternoon and he agreed to meet with us later oo during the day so that we could inform him as to what we had done up to that time and what we had said in regard to this bill. Deao Potter was here all afternoon and evening but failed to contact either ooe of us, so we had no opportuoity to discuss the situation with him before the hearing.

At the hearing the next morning, we had planned on the dean presenting all the facts in regard to a four-year school. Dean Potter got up and stated that all the members of the staff of the medical school were very much in favor of a four-year school. I have been informed by others who are in Grand Forks that the majority of the faculty are opposed to tryiog to set up a four-year medical school as they do oot believe it is feasible. That is ahout all he did say. He did not present the facts as to the cost of a four-year school, nor did he mentioo the fact that 320 beds were required. He did not give them any figures in regard to the cost of other schools.

Mr. Limond and I had the opportunity to present the cost of other schools and also the requirements as far as hospital beds are concerned. However, these facts coming from Mr. Limond and myself did not carry the weight in the committee that they would have carried if Dean Potter had presented the complete facts in regard to the four-year medical school.

We did discuss the situation with Dean Potter after the meeting and he stated that he had been instructed by his "boss" as to what he could say.

Mr. Limond prepared mimeographed sheets of the cost of the four-year school in various other states and copies of these costs were given to each member of the committee.

The ROC had a caucus the day before the bill came up for a hearing. No member of the medical profession was invited to attend. The representatives of the Grand Forks chamber of com-

○○This medical school has decided they cannot enter into this arrangement.

merce were permitted to testify before the caucus in favor of the four-year school.

The legislature was given to understand by Dr. Stucke, Senator Bridston, and many others that it would be perfectly possible to operate a four-year school under the one-mill levy with no additional expense. All the information given to the legislature except that by the medical profession omitted entirely the fact that 320 hospital beds would be required.

The bill, of course, with all this pressure and with extensive lobbying in the house by Senator Bridston and Dr. Stucke passed without difficulty. I was surprised that we were able to obtain 42 votes against the bill.

As far as I can see, the medical profession should take a passive attitude in regard to the four-year school. If we try to oppose it in any way, it reacts unfavorably towards us, so my recommendation would be that we take a very inactive attitude in either direction for the four-year school.

We have done a little preliminary investigating legally in regard to the act establishing the medical center. It would appear in a rather superficial study that it would be perfectly possible for some of the funds available to be used for scholarships for students going elsewhere for the last two years. These scholarships could be rather liberal insofar as the act is concerned. Arrangements could be made so that the students would either repay this scholarship at a low rate of interest or would be given credit for a certain amount of money of the scholarship for each year he returns to North Dakota and practices in the state. I feel that this committee should urge that such a scholarship program be set up and made available to the present classes at the university at the termination of their two-year training in North Dakota.

I should also like to suggest that it be recommended to the board of administration that they explore the feasibility of arranging with the Ancker hospital in St. Paul to set up our last two years of a medical school there. I understand South Dakota is still thinking of the last two medical years also and it might be possible that the two states could arrange with Ancker hosptial to set up a school there for the last two years in medicine.

This arrangement, if it could be worked out, would provide ample clinical material and enough hospital beds for teaching. It would also save the state the cost of maintaining a 320-bed hospital which would be at least $600,000 a year.

Dr. Cardy, the pathologist at the medical school, has submitted his resignation and I understand that Dean Potter is about to submit his resignation as dean, but is willing to stay on and teach.

I feel this committee should commend Mr. Limond for the excellent work he performed in the legislature this year.

The committee will meet in Minot on May 10th at 9:30 a.m.

H. M. Berg, M.D., Chairman

Committee on Fractures

The members of the committee on fractures did not hold a meeting during the year 1952-53; however, the policies, as carried out in previous years, have been continued.

H. J. Fortin, M.D., Chairman

Maternal and Child Welfare

The members of the committee on maternal and child welfare did not hold a meeting during the year 1952-53; however, the committee as a whole are carrying out the policies previously agreed upon.

F. A. DeCesare, M.D., Chairman

Committee on Cancer

It seems appalling that in spite of the intensive programs of the past years, we see in our offices a shocking neglect of the public to heed the danger signals of cancer. As a result, we still see the patients present themselves with a hopeless malignancy. This we must correct. Granted there is reticence on the part of the patients and frequently patient delay in presenting themselves for examination. But in a program designed to detect early malignancies, physicians can still improve their diagnostic accuracy. As the layman is being constantly confronted with the seven danger signals of cancer, so must the physician also constantly keep these danger signals in mind.

Cancer continues to be a major cause of death in North Dakota. During the year 1952, it is estimated that there were approximately 2,200 cancer cases and approximately 650 cancer deaths. This, together with the high morbidity, constitutes one of the real problems confronting North Dakota doctors and also the public. An intensive program is being carried out in North Dakota by means of the North Dakota Cancer society and the committee on cancer. Most of the members of the committee on cancer are also members of the executive committee of the North Dakota Cancer society. More and more, these groups are becoming one organization. This group meets four times a year, at which time local, state, and national policies are considered and discussed. Some of the members were present at the American Cancer society's annual meeting in New York, October 25, 1952. At this particular meeting, cancer specialists were present from Sweden, Copenhagen, and Paris, together with the specialists from the United States. One was impressed by the work being done in the treatment of cancer by means of x-ray, radium, and surgery. The University of Chicago, University of Illinois, and University of California presented discussions and results of treatment with the Van de Graaff accelerator, the linear accelerator, and the Cobalt-60 therapy machines. A summary of their results gives hope for the former hopeless cancer patient. Dr. Pack informed the public at this meting of the advances in surgery. His report represents an achievement in the field of cancer surgery. In North Dakota an intensive program is being conducted in the education the public should receive and also in the education of the busy North Dakota doctor. The North Dakota Cancer society continues to carry on a vigorous cancer program, which includes the smallest township. This is achieved by means of lectures, the showing of sound films, and the distribution of literature. Doctors in their communities are urged to respond to the call of the local chairman when called upon to give a talk at a cancer program. This talk would require no previous preparation.

Cancer seminars were conducted during years 1951 and 1952 and a similar program is planned on being presented during the month of April 1953. Participants in this cancer symposium will be Dr. L. P. Howell, Mayo Clinic, presenting a paper on "Carcinoma of the Thyroid," Dr. Thomas Pool, Mayo Clinic, presenting a program on "Malignancies of the Genito-Urinary Tract," Dr. Sidney Shapiro, Minneapolis, discussing "Malignant Tumors of the Brain," and Dr. Brian McGroarty, St. Paul, discussing "Carcinoma of the Prostate." These men will lecture in the nine principal cities in North Dakota.

During the past year an additional $10,000 was presented to Dr. Fisher of the University of North Dakota medical school for his continued research in bacteriology and an additional $4,000 was presented to Dr. Miller at the North Dakota state college. This brings a total of $93,000 which the North Dakota Cancer society has presented to the state institutions for the purpose of research in cancer.

An inquiry was sent to the seven pathologists located in the state of North Dakota regarding the number of biopsies of the skin, cervix, endometrium, and papanicolau stains received during the year 1952. The results of this survey were most enlightening and also most gratifying. All pathologists reported an increase in the number of biopsies of the skin, cervix, and endometrium. There was only a slight increase in the papanicolau stain. This probably is understandable because of the painstaking methods necessary for diagnosis. Skin biopsies during 1952 showed an increase over 1951 of approximately 6.5 per cent. Cervical biopsies during 1952 showed an increase over 1951 of approximately 11 per cent. Endometrial biopsies during 1952 showed an increase over 1951 of 13.5 per cent. It was reported, however, that there is an increased number of examinations for cancer cells on sputum, bronchial washings, and aspirations. This review certainly indicates that the busy North Dakota doctor is becoming more conscious of performing biopsies and also of the availability of laboratory methods for diagnosis.

The state health department continues to comment on the fact of the lack of cooperation on the part of the physicians to report and register cancer cases throughout the state. The attention of the medical profession should be directed to the necessity of reporting cases through their local health officer. Forms are available through the state health department for the purpose of reporting cancer cases. It has been commented by several doctors that possibly the forms should be more streamlined. This will be taken up with members of the committee during the present year and any other possible means to increase the reporting of cases will be reported at a later date.

The North Dakota Cancer society announces that their quota for the year 1953 is $92,000. This will not be raised by wishful thinking but by diligent and enthusiastic "bell pushers" and personal solicitations. Space does not permit a story of each county unit's plan for house to house or porch to porch canvass. The North Dakota physician is urged to cooperate with the county workers in helping the society obtain this goal. In the past, the North Dakota State Medical association has given its complete endorsement to the program and it is hoped that their endorsement will continue.

It was with much regret that the resignation of Dr. L. W. Larson, as president of the North Dakota Cancer society, was accepted by the executive committee. Dr. Larson has been one of the founders and builders of our state organization. His numerous duties as a member of national committees, especially as a member of the board of trustees of the American Medical association and the American Cancer society, have forced Dr. Larson to relinquish his cancer work in North Dakota. A fitting tribute to his efforts for the North Dakota Cancer society was instituted recently by the establishment of the "Leonard W. Larson Lectureship," which was first inaugurated at the meeting of the North Dakota Obstetrical-Gynecological society at Fargo in September 1952. Dr. Gardner, professor of obstetrics-gynecology at the Northwest University was the first doctor to present the "Leonard

W. Larson Lectureship." Dr. Gardner presented a paper on "Carcinoma of the Ovary." Dr. E. J. Larson of Jamestown has been elected president of the North Dakota Cancer society and already he has taken a vigorous hold of the reigns and we are looking forward to more successful years under his leadership.

CARROLL M. LUND, M.D., Chairman

Public Policy and Legislation

The committee on public policy humbly wishes to present this report.

Various attempts have been made to meet during the winter but have failed to get the entire committee together due to the "flu" or weather conditions. Members of the committee, however, have been contacted by phone and the bills of interest to the medical profession introduced in the past legislative sessions were discussed. Our executive secretary, Lyle Limond, acted as lobbyist for the North Dakota State Medical association and kept us all well informed as to what was transpiring at the Capitol. He gave aid to all public health bills where it was deemed advisable plus securing aid of our president, Dr. O. W. Johnson, on the special education bill where he appeared before the senate appropriations committee.

Representatives Beede of Elgin, Toussaint and McLellan of Fargo carried the fight against the four-year school by 1956. Dr. H. M. Berg of Bismarck appeared before the house committee on state and federal government on the medical school bill as the chairman of our medical education committee. Dr. Berg's committee report will carry the full story of this bill.

On September 26, 1952, the first medical-press-radio conference was held in Fargo. Representatives of the radio and press from Grafton, Park River, Grand Forks, Hillsboro, Fargo, Valley City, Jamestown, Wahpeton, and many of the smaller intervening cities had an opportunity to meet and talk to doctors from this same territory. The meeting started out with an informal social hour during which time it was possible to really meet these people who are so vital to the well-being of the medical profession. Following the social hour, all enjoyed a wonderful banquet, not sitting in groups talking shop but sitting next to the members of the press and radio discussing common problems. This was followed by two short prepared speeches and the remaining time was spent with a question and answer period which I'm sure was very instructive to both the lay and professional groups. The comments received after the meeting was over were very good and I would suggest that other conferences of this type be held by the large district medical societies.

Due to the fact that it is so difficult at times to contact various members of the legislature, it is suggested that there should be a different set-up for the committee on public policy and legislation. One suggestion I have to offer is that 1 doctor be appointed from each of our 49 legislative districts with a central committee of 6 or 8 doctors. This group is to act on all matters of legislation and then have a separate committee for just public relations or public information. I feel this should be discussed by the house of delegates and, if deemed possible, put in operation before the legislature meets again.

It is also our suggestion that the council be liberal in their appropriation to the committee on public relations, for it is only through the dissemination of information that the medical profession will again come into the good graces of the public.

The executive secretary will list all the contacts made with groups and individuals—all of which is in the field of public relations. The committee on public policy appears to be well pleased with the work of Lyle Limond.

O. A. SEDLAK, M.D., Chairman

Annual Report of Delegate to American Medical Association

Your delegate attended all sessions of the house of delegates at the annual session, June 9 to 13, in Chicago, the clinical session held in Washington on Saturday, March 14, 1953, and in addition, he has attended all meetings of the A.M.A. council on rural health, including the national conference on rural health in Roanoke, Virginia, February 25 to 28, 1953. At the Denver session, he was appointed a member of the committee on extension of hospitals and other services under the council on medical service, and has attended meetings of this committee. Dr. James R. Reuling, speaker of the house of delegates, has intimated that in the future, no delegate who is a member of a council will be appointed to a reference committee for the reason that his council may have business before that committee. Hence, in the future, your delegate will probably not be assigned to a reference committee.

The business of the house is almost entirely conducted by reference committees in a manner similar to that of our state association. I would like to point out that any member of the A.M.A., as well as officers, members of councils and delegates, have the privilege of expressing their views on any subject in which they are concerned before the reference committee which has that subject under consideration. There are no closed hearings of reference committees and any member of the association is welcome to attend as an observer or to participate.

The complete report of the annual session held in Chicago appears in the Journal of the American Medical association, June 28, 1952, page 851, and in succeeding issues of the Journal. The report of the Denver clinical session appears in the J.A.M.A., Decemebr 27, 1952, page 1676. A report of the March 14 special session will probably appear in the March 21 or 28 issue.

I will briefly mention a few of the more important matters under consideration and the general trends in policy of the A.M.A. at the present time.

1. The activities of the Magnuson commission were highlighted at the Chicago session because of a resolution introduced from Illinois condemning, in no uncertain terms, Dr. Magnuson for his uncalled-for attacks on the American Medical association. Considerable bitter discussion occurred here which indicated a fundamental difference of opinion between the majority of the members of the association and the members of the Magnuson commission. I attended a regional session of this commission held in Minneapolis, and I read a brief report as representative of the Nortb Dakota State Medical association. The recommendations of the committee appeared in late November and are being followed by a report of the testimony submitted. Most briefs submitted represent the opinions of many people which were well known for many years prior to this commission investigation. In general, as predicted, nothing new was unearthed and the recommendations and conclusions follow the familiar line of more and more federal grants for this, that, and the other medical activity. The facts of the matter are that no new information of any value was unearthed by this investigation; that factual and detailed information presented by recognized medical authorities was mostly disregarded; that the opinions of labor leaders, advocates of social change, and others were assigned a great deal of importance. In summary, one may say that the report and conclusions are a hodge-podge of sugegstions reflecting the preconceived opinions of many persons who, in general, favor increasing the power of the central government and have no other solution to offer for any economic problem other than increased taxes and increased federal participation in payment for that particular type of service. There is an excellent discussion of this entire report in the J.A.M.A. March 21, 1953, by Frank Dickinson, Ph.D., head of the bureau of economics of the A.M.A. He suggested that the entire report should he filed away under the heading of Creeping Socialism.

The house of delegates has been and will be, concerned with several other important present-day problems. They are:

1. Doctor draft legislation. Many members feel that the present doctor draft law is highly discriminatory and unfair and there is every good reason for them to adopt this attitude. At no otber time, and in no other country that one can think of, has it been necessary to enact such a piece of legislation. The present law, public law 779, expires on June 30, 1953, but undoubtedly further legislation will be necessary to provide adequate medical care for the armed forces. The A.M.A. has been conducting a study with the intention of finding out how much actual time many doctors are spending giving services to dependents of service personnel. I think we all agree that it does not seem at all fair to remove doctors from civilian life by process of law and then compel them to give their services to civilians, even if they are dependents of military personnel. The position of the A.M.A. is that we recognize the paramount necessity of provision for sufficient doctors to care for the armed forces, but we are concerned that the very best utilization of these men's services be required.

2. Care of veterans with non-service-connected disability in veterans hospitals. A great deal of discussion occurred at the Denver meeting concerning this problem, hoth by members of the house and hy others. The furnishing of medical care to veterans with non-service-connected disabilities through the facilities of the Veterans administration has grown to be a very large activity of that organization. Depending on how figures are interpreted, the percentage of veterans in VA hospitals with non-service-connected disabilities varies from 66 to 30 per cent. The actual law, public law 312, states that veterans with non-service-connected disabilities may be admitted to Veterans administration hospitals for treatment, provided facilities are available and the veteran is unable to pay for this treatment privately. The crux of the matter is that no attempt is made to determine whether or not the veteran is ahle to pay for this treatment; hence, in effect, it means that all veterans may be admitted to a VA hospital, on request, if beds are availahle. All doctors will agree, that this is an undesirable situation and should not really be a proper emolument of service in the armed forces any more than food, clothing, or shelter should he. However, this is a practice which has been going on for many years and is part and parcel of the program of the leading veterans organizations. It would he impossible to affect any change in this situation without the support of the major veterans organizations and a major portion of the taxpaying public. The present approach to the problem is to endeavor to

enlist this support. It seems unlikely that much success will be attained in the near future.

3. Voluntary health insurance. It is absolutely necessary that every effort be made to continue the expansion and proper use of voluntary health insurance. While agitation for compulsory health insurance is not now as active as previously, it is merely dormant and may rise again at any time.

4. Current unfavorable publicity emanating from the college of surgeons through its director, Dr. Paul Hawley, has stirred up a great controversy within the profession and has given us a great deal of very poor publicity. So far, discussion of this subject has been kept out of the house of delegates, but resolutions may eventually be brought in there. The problem is essentially one of how you are going to go about inoculating ethical and moral principles into some members of our profession.

The house of delegates met in special session in Washington in the Statler hotel, March 14, 1953, to consider the proposed reorganization of the Federal Security administration. The house was addressed by President Eisenhower, Senator Taft, Representative Walter Judd, and various officers of the association. For some 80 years, the A.M.A. has been on record as favoring an independent department of health with cabinet status. This position has been reaffirmed on many, many occasions. We also opposed on two occasions, President Truman's proposal to elevate the Federal Security administration to cabinet status. At this session the delegates unanimously approved a resolution presented by the board of trustees which, in effect, gave A.M.A. approval to President Eisenhower's proposal for reorganization of the Federal Security agency with elevation to cabinet status. This reorganization plan differs from preceding proposals in several important particulars. From our point of view the main change is that there is a provision for a special assistant to the cabinet secretary, on health and medical affairs, to be appointed by the President from persons who are recognized leaders in the medical field with nongovernmental experience. This individual, in effect, is to represent the federal security administrator in all matters pertaining to medical affairs. This is a nonadministrative post and will be concerned with all matters of policy in health matters in which the federal government is involved, either within the various agencies of the government, with the states, or with other countries. It is anticipated that the doctor appointed to this position will be one who is approved by the A.M.A.

For the first time in over twenty years, we now have an administration in Washington, pledged to good government and one which is desirous of cooperating with, and having the cooperation of, the organized medical profession. This gives us a tremendous opportunity to proceed with constructive programs and to make our influence a power for good in the affairs of the nation. Greedy and unethical practices by individual physicians are the main factors which will dilute and diminish this opportunity for service to the country as a whole.

W. A. Wright, M.D., Delegate

Medical Center Advisory Council
(1953)

The North Dakota Medical School is at the crossroads. This is due to the culmination of numerous factors, the most recent of which is the ill-advised passage of Senate Bill 184 during the last session of the legislature. This bill, which is now a law, provides that a sufficient portion of the funds provided in the one-mill levy, "shall be retained by the board of higher education to permit the establishment of a third year course in medicine at the center not later than 1955, and a fourth year course not later than 1956." In other words, the board of higher education has a mandate to establish the third year not later than 1955, and the fourth year not later than 1956. The proponents of this legislation were either ignorant of the facts in the case, or were unwilling for political reasons to consider them. According to the reports I have received, the university administration did not provide the legislators with factual data concerning the present situation of the medical school nor did they emphasize the difficulties which must be overcome before the third and fourth years can be established. Attempts made by representatives of the state medical association to present the facts in the matter were entirely unsuccessful. An impasse has therefore been reached in which the board of higher education must, according to this law, find ways and means of establishing the third year course not later than 1955, and the fourth year course not later than 1956, regardless of problems which must be solved prior to those dates and which, at the present time at least, cannot be solved with the finances at its disposal and the hospital facilities available in Grand Forks for teaching purposes. This recent development, plus several other factors, has contributed to the present impasse, as a result of which one of the leading professors in the medical school has resigned and, I am informed, Dean Potter intends to resign his deanship, but is willing to stay as professor of physiology. The medical school, therefore, faces the distinct possibility of reverting back to the situation of a few years ago in which it will be understaffed and its approval by the accrediting agencies will either be withdrawn or the school will be placed on probation.

What about the medical center advisory council? Has it done nothing to prevent the impasse which has developed? These are logical and legitimate questions. In answering them it should be understood that the medical center advisory council is a legally constituted body with very limited power. It is purely *advisory*. The final responsibility for the medical school rests in the board of higher education and in the university administration. Through resolutions, the advisory council supported the development of the two-year medical school to a point where it finally received unqualified approval on the part of the accrediting agencies. It has supported the policy of utilizing a large portion of the funds collected by the one-mill levy for the construction of a new addition to the medical building and for the equipment of the entire building. It has recognized that the passage of the amendment to the constitution of the state providing for a one-mill levy for the medical center carried with it the implication, at least, that North Dakota would ultimately have a four-year medical school. However, the advisory council unanimously agreed on a number of occasions that the first problem was to gain approval for the two-year school and then to proceed in a careful and orderly manner to the development of a four-year school, if at all possible. The following resolution was passed by the advisory council at its meeting on January 10, 1953:

> "Be it resolved that the medical center advisory council express its approval and endorsement of the progress which has been made in the improvement and accreditation of the two-year medical school, and that when the present improvements to the physical plant are completed, the proceeds of the mill levy should be carefully husbanded and accumulated looking forward to the ultimate establishment of a four-year medical school."

This resolution is merely an expression of realism in contrast to the ill-advised legislation referred to above which sets a deadline for the development of the third and fourth year courses at the medical school. It is most regrettable that the majority of the legislators, many of whom were responsible for the passage of the medical center law in 1945, which provides for the medical center advisory council, were unwilling to take the advice of the council in this most important matter.

Ever since the medical center law was passed, the association has been placed more or less in the position of an unwilling bridegroom at a shotgun wedding. It has official representation on the advisory council, with all the implications thereto, and yet it is perfectly evident that the university administration considers the council as merely an "advisory" body. Certainly it is a matter of record, in view of what transpired during the recent session of the legislature, that the university administration paid little attention to the resolution passed by the council as quoted above. A majority of the legislators acted in a similar manner.

In the discussion of the situation at the medical school, it would be unfair to disregard the attitude and actions of the board of higher education. This board has pursued a course of intelligent realism. Dr. A. D. McCannel is undoubtedly responsible, in part at least, for the board's attitude toward the development of a four-year course at the medical school. As a result, he has been subjected to criticism directed toward his motives, knowledge of the problem, and even his integrity. Perhaps this is the price one must expect to pay for devotion to duty and the sacrifice of time and money for the common good without hope of reward. If such is to be the fate of those who serve our citizens in a voluntary capacity, the time will soon come when all the affairs of our state will be controlled by men and women who serve for personal aggrandizement, financial reward, or political advantage. Your representative on the advisory council has been placed in a position similar to that of Dr. McCannel, a fact which is pertinent only in that it emphasizes the seriousness of the problem in the medical school and the urgent need for the association to adopt a definite policy concerning it.

The time has arrived when the North Dakota State Medical association should make a thorough and careful study of the medical center law with a view toward better implimentation of the law or possibly to amendments. Also, the association must adopt a definite statement of policy regarding its attitude toward the medical school. It has two choices: (1) A hands-off policy; (2) An aggressive policy in which its opinions will be given careful consideration by all those concerned with the control and development of the medical school (including politicians).

Unfortunately, a large percentage of the citizens who voted for the one-mill levy did so with the expectation that a four-year medical course would be developed soon, thereby relieving the alleged shortage of physicians, especially in the rural areas. It is only natural that they should be disappointed because the third and fourth year courses have not been started. They have not been convinced that the first problem was to develop the two-year school to a point where it would be accredited. For these reasons, in adopting a policy toward the medical school, our association faces a difficult problem in public relations. If the association adopts a hands-off policy, it will be criticized in the event that

the present two-year school deteriorates, or, the third and fourth year courses are started and result in a substandard school which will not be approved by the accrediting agencies. If we follow the second course and adopt an aggressive policy based on sound and realistic thinking, we will have to convince the politicians in the state, and also a large group of citizens that we are not trying to prevent North Dakota boys and girls from obtaining a complete medical education in the state. The course we follow must be determined by what we honestly believe to be in the best intrest of the public at large.

What are the true facts concerning the proposal to start the third year course not later than 1955 and the fourth year course not later than 1956? The financial statement as submitted by the business manager of the university to the medical advisory council, indicates that the annual return from the one-mill levy averages about $550,000. The present budget for the two-year school amounts to $375,000. This leaves a balance of $175,000, most of which will be needed for purchasing equipment for the new addition to the medical building during the fiscal year 1953-1954. This balance of $175,000, which is based on the assumption that expenditures do not increase and tax collections hold up, would not be sufficient to defray the additional expense for the numerous clinical professors and teachers of less academic rank who would he necessary to teach the junior and senior students. Thus the first difficulty is the lack of adequate funds. Will the legislature in 1955 be willing to appropriate additional funds to cover the greatly increased cost of maintaining a full four-year medical course? It is extremely doubtful that it will do so in view of the fact that a majority of its members are convinced that a four-year course can be maintained by the one-mill levy, in addition to the growing antagonism of the public toward increased taxes.

A second and equally important obstacle is the lack of adequate teaching facilities in Grand Forks, especially for the junior class. The accrediting agencies insist that there shall be a minimum of 8 teaching beds for each junior student. This would mean 320 teaching-beds for a junior class of 40 students. Is the state of North Dakota prepared to huild a 320-hed charity hospital in Grand Forks at a cost of 6 to 8 million dollars? The answer is: NO! Thus it can be easily understood that the third and fourth year courses cannot he started in the time allotted by the last legislature because of insufficient funds and lack of teaching-bed facilities. Those legislators who talked loud and glibly about the medical trust, medical hierarchy, and the determination of the doctors of the country to limit the number of medical students and therefore the number of practicing physicians, disregarded these simple facts. They pointed to the many fine hospitals in the state, and the clinics and individual practitioners who would be most willing to cooperate in a preceptor teaching program. They brushed aside the fact that the accrediting agencies insist on an adequate number of available teaching-beds for the junior students. They were not even informed by Dean Potter that plans for the instruction of the members of the present sophomore class in physical diagnosis in several of the larger hospitals in the state, as recommended by Dean Lewis's committee to meet the demands of the accrediting agencies, had not been completed. In fact, the plans are not complete as of April 10, 1953, in spite of the fact that the schedule calls for the sophomores to begin this instruction on May 5, 1953.

How can the present prohlem be solved? If recent history repeats itself, the graduates of the present two-year school will probably have little difficulty in the future in gaining admission to other schools for the third and fourth years of instruction. This is predicated on the assumption that the admission standards will be maintained at a high level and the two-year school will retain unqualified approval by the accrediting agencies. If this is true, and it is assumed that the state of North Dakota is obligated to provide the third and fourth years of instruction but cannot do so within the state, the only alternative is either to enter into an agreement with some nearby four-year medical school, or to suhsidize, in part or in full, the cost of tuition at any medical school which will accept the student. There is reason to helieve that the negotiations which have been carried on with nearby schools to take all, or a part, of the class for the third and fourth years, have not been pursued with any degree of enthusiasm by the university administration. Either plan, or a combination of both, would necessitate transferal of medical center funds direct to the affiliated school or to the student. Some individuals who are familiar with our laws doubt that state funds can be transferred to an education institution in another state, but they seem agreed that the funds could be dispersed in the form of a scholarship. A few states, finding themselves in similar circumstances, have made state funds available to the student as a loan with the signed agreement that the loan will be cancelled if the student returns to the state and practices for a definite number of years in a locality where he is needed. This plan has merit and should be given careful consideration by this association and also by those who are in charge of the medical center funds and administration.

RECOMMENDATIONS

1. That the association reaffirm its policy toward the medical school, which is: (a) that the present two-year school be strengthened so it will maintain its accreditation; (b) that the school be enlarged to a full four-year school *when* and *if* funds and teaching facilities, including hospital beds, are available; (c) that the physicians of the state be encouraged to cooperate in every way possible in the development of a clinical teaching program.

2. That the association request a joint conference in the near future with the university administration, board of higher education, and the medical center advisory council for the purpose of reviewing the situation in the medical school and reaching an agreement on a sound and practical plan of action.

L. W. Larson, M.D., Member
Medical Center Advisory Council

SPECIAL COMMITTEES

Emergency Medical Service

The committee on emergency medical service has held no meeting in the year 1952-53. The following information has been formulated through written inquiries and telephone conversations of the chairman with other members of the committee:

Civilian defense preparedness in North Dakota slumped relatively much during the late fall and winter of 1952-53; in fact, all observation posts were discontinued during the winter, and the one held early in the fall were successful only in the larger centers, such as Minot and Fargo.

There were no catastrophes of any type during the 1952-53 year. No floods and no Red Cross emergency service except the blood donor program, which was met during the year by means of a special railroad coach run by the Red Cross throughout the state and several thousand pints of blood were obtained for the United States army. It is recommended that in the future, Red Cross blood donations be approved through each district medical society. The reason for this is that on several occasions during the 1952-53 season, local blood procurement for our state plasma program conflicted entirely with the Red Cross blood donor procurement. This happened at Rugby, and the turnout for the local blood plasma state program was very poor.

It is again reiterated that since North Dakota has a tremendous square mile area and a very sparse population, and since major communities are small in size and since there are no military targets, that probably the only medical service that the state could render in a severe general emergency such as war and bombing of the larger centers of the United States would be to serve as a supporting area for larger centers such as Minneapolis and for the stockpiling of any medical defense material. Nothing has been done about this to date. However, the hospital facilities of the state could quickly be made available for any transfer of casualties from the larger centers.

C. G. Johnson, M.D., Chairman

Industrial Health

The recent discovery of oil in the Williston basin, no doubt means an accelerated industrial development for western Nortb Dakota, and with this development may come an increased importance of this committee which has been semi-dormant for a number of years. The possibilities of the increased use of lignite coal in chemistry add to this industrial growth.

The national council of industrial health of the A.M.A. continues to be a vital organization and keeps in frequent communication with your chairman by newsletters with the various programs they sponsor.

It is again urged that each district society devote one meeting each year to some phase of trauma.

C. J. Glaspel, M.D., Chairman

Committee on Mental Hygiene

This committee met only once during the past year but feels that two of its three recommendations of May 1952 are now being expedited, namely:

1. Follow-ups on patients sent to the Jamestown state hospital should be sent back to the referring doctor immediately. This is being instituted by Dr. Thomas L. Gore (now clinical director, but on July 1, 1953, is to become superintendent of the Jamestown state hospital) with the hiring of a social worker to send back referrals to the private physician.

3. Nurses should receive their psychiatric training in the state of North Dakota at the Jamestown state bospital instead of going out-of-state. This recommendation will be met starting July 1, 1953. A director of psychiatric nursing and an assistant director of the school of nursing are to be hired. A three month course in psychiatry will be offered to nurses. About 50 nurses will be trained quarterly after existing contractual agreements are terminated. $300,000 was appropriated by the 33rd legislative assembly for a nurses residence.

2. Members of the board of administration to meet with this committee in order to acquaint the board members as to what psychiatric care is. Nothing came of this recommendation, but

a definite invitation has been extended this committee by Dr. Gore to meet with him and the board after July 1, 1953.

The committee now feels, that with Dr. Gore's arrival, the Jamestown state hospital is beginning to avail itself of the trained doctors of medicine in private practice in North Dakota for aid in improving the medical facilities at the institution.

The following are new recommendations by the committee:

1. The North Dakota State Medical association should become a life member ($50) of the North Dakota Mental Health association. Our association should urge those doctors of medicine interested in mental health to become active members ($2) of the North Dakota Mental Health association.

2. Efforts should be made to influence the authorities to change the name of . . . . . County Insanity Board to . . . . . County Board of Mental Illness.

3. The North Dakota State Medical association should support the psychiatric clinics which are being planned.

4. The rehabilitation of patients at the Jamestown state hospital be considered and a plan of placing patients in industry outside of the hospital be developed.

The committee hopes to make a study of the facilities at Grafton and Jamestown this coming summer or fall.

L. H. Fredricks, M.D., Chairman

SUB-COMMITTEE ON MENTAL HEALTH

Your sub-committee on mental health met at the state Lodge in Minot on December 21, 1952. The property operated by the state alcohol commission and managed by Mr. Truman Wold was inspected and visitation made with several of the guests, prior to the main meeting.

It was revealed that since the opening of the lodge, February 15, 1952, until November 30, 1952, a total of 154 patients had been treated and discharged. The average cost per patient day amounted to $7.20.

Mr. Wold's summary of patients discharged was as follows:

Persons totally refraining from use of alcohol since discharge	71 (46.1%)
Persons suffering single relapse and return to total sobriety	35 (22.7%)
Persons suffering multiple relapses and return to total sobriety	9 (5.8%)
Persons experiencing no radical change in drinking habits	39 (25.3%)

The committee felt that although this was a most gratifying report and reflected the good work being done by Mr. Wold, there had been no provision for the medical treatment of the acute alcoholic. The use of drugs, intravenous therapy, insulin therapy, the benefit of psychiatric consultation, and so forth, had not been provided and it was their recommendation that these increased facilities be made available.

At this meeting, the committee extended the administrator its full support in requesting the legislature to expand these facilities by providing a large enough appropriation to adequately house and treat these patients. As you know, although the legislature recognized the value of this alcoholic treatment center, it could not agree on a method of providing funds for the institution. Due to this failure on the part of the legislature, the treatment center has been discontinued.

It would seem that the alcoholic program should share proportionately in the welfare funds collected through the state sales tax. This fund now is in excess of $14,000,000 and is not necessarily supervised through the welfare department.

It was the hope of the sub-committee that doctors attending the state medical meeting would avail themselves of the opportunity to visit the lodge. Now it is their hope that the doctors will make it their business to convince their local representatives to make provisions at the next session of the legislature for adequate care of these mentally ill people.

D. J. Halliday, M.D., Chairman

Committee on Displaced Physicians

The committee had no formal meeting during the past year. The state board of medical examiners meets twice a year, and whenever else it deems it necessary, reviews reports on all displaced physicians. During the past year, charges against several D.P.'s were heard, but no disciplinary action was deemed necessary.

The D.P. program at present is closed, that is, no new D.P.'s are allowed to come into North Dakota at present with the exception that a limited number will be allowed to practice in the various state institutions. I do not believe that any new D.P.'s have been admitted during the past year.

O. A. Sedlak, M.D., Chairman

Committee on Diabetes

The committee on diabetes again this year organized the annual diabetes detection drive as part of "National Diabetes Week," with the cooperation of the American and North Dakota diabetes associations. This committee is largely composed of representative members of constituent district medical societies of the state medical association.

The members of the committee for 1952-53 are as follows: E. J. Beithon, Wahpeton; Martin Conroy, Minot; G. D. Icenogle, Bismarck; T. E. Pederson, Jamestown; W. H. Gilsdorf, Valley City; Martin Hochhauser, Garrison; A. K. Johnson, Williston; R. M. Fawcett, Devils Lake; F. M. Melton, Fargo; C. M. Graham, Grand Forks.

According to established policy, each district medical society was asked to vote for or against having its own local detection drive. Response was very poor in this regard. Throughout the state a total of only 6,414 free urine tests were performed and 122 cases of glycosuria were discovered. To date 10 of these "positives" have been proven to have diabetes, 1 of which was previously known. (A number of final reports have not as yet been received.

Eight cities participated in the drive—November 16-22, 1952. Local drives and respective chairmen of committees on diabetes detection were as follows:

Lakota, J. A. Engesather; Williston, A. K. Johnson; Maddock, W. S. Pollard; Devils Lake, R. M. Fawcett; Grand Forks, C. M. Graham; Jamestown, Tom Pederson; Garrison, Martin Hochhauser; Minot, Wm. Ensign and Martin Conroy.

There are several reasons why the 1952 detection drive in North Dakota was not as successful as previous campaigns.

1. Retarded interest in diabetes detection.
2. Some societies thought it was too much work.
3. Publicity much less intensive than previous year.
4. Some groups believe a drive every two years would be preferable to an annual drive.
5. Several societies anticipate an intensive drive next year.

It is felt that a new approach to rekindle enthusiasm in diabetes detection in North Dakota is needed.

Comparison of our previous figures illustrates this. The use of Dreypak as a detection means might give the program a "new look" and may elicit a tremendous response both on the part of the medical profession and public. The principle of Dreypak is as follows: After reading the instructions on the Dreypak, the patient merely delivers the dry specimen of urine on the filter paper to a collection point. This eliminates the unpleasantness of delivery of the urine specimen itself. They can then be processed by the hundreds simply by dipping the filter paper into boiling Benedict's solution. This results in a color reaction change on the filter paper similar to the color change incident to Benedict's test in the test tube. Efforts are being made to obtain this method of urine testing for use in the drive for the year 1953.

E. A. Haunz, M.D., Chairman

Committee on Nursing Education

As chairman of the committee on nursing education, I would like to make the statement that this is not a solution for our nursing problems in the state. It is only a resume of the facts and may be of some value in the future evaluation of the present situation. Inasmuch as it is very difficult for the committee members to meet without traveling a long distance and a central location cannot be definitely arranged at the present, I see no reason for asking members of the committee to meet and discuss a problem of which we have so little information. So little can be done about it at the present time that I have not insisted that the members meet up to the present time. It may be well that we meet just before the medical society to discuss problems which may arise in the ensuing year.

The medical profession, nursing profession, and the hospitals make up a team working for one purpose—to care for the sick and to promote preventive medicine. The three groups are so closely interrelated that changes which affect one group are of concern to all three groups. The care of sick people will be only as efficient as the cooperation of the three groups and anything that weakens one will weaken the entire program. Changes have been proposed within the nursing profession which are of concern to the members of the medical profession of this state, as well as to all states in the central United States. Two of these are thought to be of sufficient significance to the medical profession to devote study by both sides for the proposal of the same. One is a 40-hour week, five-day work week for registered professional nurses which was just voted on in North Dakota as well as in other states in our immediate neighborhood. The other is a modern trend toward emphasis on larger university training schools for nurses with a corresponding de-emphasis on the training schools in the smaller hospitals which do not confer academic degrees in connection with certificates of eligibility for nurses. It is hoped that members of the medical profession will acquaint themselves sufficiently to inform themselves of the facts in order that they have a sound basis on their own opinions as to what is best for the patient. For in the final analysis, the nursing profession as well as the medical profession exists for one purpose only, that is, to care for the patient. It is therefore that I take this opportunity to clarify and give you some information which is now available to me as a result of studies and meetings held at Kansas City only recently, on September 28, and another meeting which will be held very

shortly in the midwest area, probably after the first of January, 1953, to cope with this problem.

Only recently, in June 1952, at the Atlantic City convention of the American Nurses' association, a resolution was drawn up which in a few words asks all nurses in the district and state associations to work for an immediate implementation of the 40-hour week as set forth in the resolution passed by the nurses' association on that date. It promotes the 40-hour week as an accepted basic work week for the majority of employed groups throughout the United States. In other words, it is comparing the nurses to the other laboring units that are now clamoring not only for a 40-hour week (which they have long since had), but for a 30-hour week. If the nurses wish to belong to the professional group and not to the employed labor group, they must act as such and not act as a lahoring group of people. A 40-hour week may not be enough time for our nurses to work to give our patients the kind of care they require—plain ordinary bedside nursing care is what the nurses are bere for. It is very probable that we can do nothing to prevent the nurses of North Dakota from demanding and getting this resolution through their associations. While this resolution is good and proposes a much desired shortening of the work week, it also poses many other problems which must he viewed carefully in analyzing the relative merits of its adoption.

Hospitals for many years have been operated as nonprofit organizations for the purpose of rendering the most economical service to the community which they serve. To this end hospital administrators, doctors, nurses, and other categories of hospital personnel have given their support wholeheartedly. However, bospital costs over the last ten years have more than tripled, and in some instances have increased as much as five to six times, due to the high cost of drugs, food, dressings, and personal services to the patient. It has heen hut a few years since graduate nurses were employed at $50 a month for 12-hour shifts of nursing care, and in some cases on a seven-day week basis. We realize that this practice has had to he modified in caring for the increased numher of acutely ill patients that we have in our hospitals today.

The ultimate consumers of hospital service, third party payers, commercial insurance companies, and so forth, have heen faced with the hurden of meeting these increased costs of hospitalization.

The present demand for additional well-trained graduate nurses is prohably our most acute problem. The 40-hour week resolution refers to this shortage hut does not pose any real solution, as hospitals are currently employing nurses on an hourly and daily work schedule to meet their own conveniences. Our need is to attract more students to become educated in nursing and to attract more graduates from other states and from our own state to carry on the professional work for which they are trained. It is our helief that the cause of nurse shortage in the midwest and in North Dakota particularly can better he dealt with in local communities in a program such as pilot studies in personnel relations will avail us.

The second major prohlem concerns the resolution to regulate the worikng time nf nurses to 40 hours in five successive days within a week. Here again much might be said both for and against it, hut little without prejudice. It is easier for the average physician to understand the effort to raise educational standards than it is for bim to justify the passage of this resolution. He can accept the fact that many nurses have not heen paid a fair rate for the services they have rendered. They have worked long hours and have consistently given more than they have received. But to a degree, at least, the same applies to the physician. He knew hefore he entered the practice of medicine that his working hours would be long, that heavy demands would be made upon his time, that he would perform many services for which he would never he paid. He knew before entering medical school that the life of a doctor is not a well regulated existence. In selecting medicine he accepted the hardships voluntarily, considering them of the less than major consequences. Presumably, other vocational opportunities were open to him, some which might have provided greater security, more regular hours and many other desirable features. However, knowing all these things, he selected medicine for whatever reasons he may have had, and in that knowledge he takes the difficulties together with its advantages and without complaint.

It is perhaps not completely unfair for us to suggest that as an important segment of the healing professions, the nurse is in a comparahle position. She too accepted nursing hecause of opportunities, hut together with these advantages she also accepted its liahilities. To have her now declare that her service to mankind will be rendered within a 40-hour, five-day week is something short of the ideals upon which the nursing profession was founded. And quite possibly no argument can be presented to completely erase this thought from the mind of the physician.

The above comment is completely apart from the economics involved. The nurses should not be expected to work for unreasonahle wages; and we are not asking them to work that way. The physician, to be fair, must be concerned over the factor that will render assistance toward improving the financial situation of nurses wherever conditions demand improvement. This can only be accomplished without the formality of regulations which, even when self imposed, can only tend to reduce a profession from a high position to the status of a trade union. The benefits to be derived from the passage of such a resolution, although material, might well bring with them regulations and greater problems than any of those currently existing which they bope may be corrected.

A statement that 9 per cent of the current nurses having academic degrees has been studied. Since they generally fill teaching, supervisory or public health assignments, that proportion appears about right in relation to the total number of nurses. Should educational requirements be raised to increase that percentage, the shortage of nurses for hedside care will become greater than the present. Coupled with this situation and the reduction of students hecause nursing schools are being closed, a currently difficult condition assumes the proportion of disaster.

The dilemma rests, therefore, in the lap of the nursing profession. The doctor is admittedly concerned, but awaits the decision by the nurse as to whether she or some other group will perform the nursing services for sick people. Bedside care of sick people is essential, so hospitals and physicians will bave no choice should the current resources be eliminated but to maintain such service from outside the nursing profession. The prospect is not particularly inviting, since nursing care should be provided by only trained personnel—professional persons of the type tbat are educated in schools of today are considered inadequate. Should the nurse prefer the glamor of teaching, the problem of shortage will have been solved since teaching requirements will be impressively reduced. Should the nurse accept the principle that patient care is nursing service, then she must further assume some of the responsihility for its lack. She must turn one way or the other, and neither course appears carpeted with roses.

The physician and nurse work as a team. They serve where they are needed and for whatever hours such care is required. They each possess a devotion to their profession that transcends interest in a timeclock, and count service as a considerable reward for their effort. This is not to infer that economics and educational standards are of no concern. It is my opinion that the national association has directed the North Dakota nurse, and those of the midwest states, to follow a course apart from hospital aod medical viewpoints. Her prohlem is now to decide which will provide her the hest opportuoity for service. It involves her personal future, the future of her profession as well as with the puhlic. She has given the subject a great deal of thought, and it is sincerely hoped that her decision will prove to be wise. North Dakota has 12 accredited schools of nursing as of March 1, 1952. The daily census varies from the smallest of 60 patients to the largest of 205. The students involved are from the smallest of 18 students to the largest of 156. We have a total of 1,429 heds in accredite schools of nursing in North Dakota and a total of 886 nurses registered in these schools as of March 1, 1952. "The ultimate purpose of accreditation of schools of nursing is the improvement of nursing service." This is a copy of the first sentence of the section on purposes of accreditation as outlined hy the National Nursing Accrediting service, a program established hy 6 of the national nursing organizations. At the recent convention in Atlantic City, these organizations approved a merger resulting in the continuation of 2 of the organizations, the American Nursing association and the American Association of Industrial Nurses.

The purpose I stated is a worthy one and deserves the interest and active support of all health groups and the general public in a combined endeavor towards its achievement. Before any group or combination of groups, especially the professional groups, can intelligently plan a solution to a problem, they should carefully determine if their proposed plan of action will accomplish in the best effective way, if desired. In other words, we must be sure the nursing accreditation program as presently carried on, is goiog to provide more and hetter patient care both now and in the future, rather than have it merely result in better nursing education.

In 1949 there were 21,400 student nurses graduated from all schools of nursing in the United States. In 1950 there were nearly 26,000 graduates. Using the average, there are approximately 29,500 graduates for 1951. Only 50 per cent of these graduates remain in active nursing more than two or three years. Our most current numher of graduates in 1951, that is of the 29,500 student nurses who are graduated in 6,800-plus bospitals in the United States graduating about 4½ nurses for each year for each hospital in the United States or 86 per cent of whom are educated in hospital schools of nursing, only 50 per cent remain in the hospital nursing field. In spite of this overwbelming evidence, our greatest need today is more nurses. The accrediting progran has announced that its list of fully and temporarily accredited schools will be published and widely distributed so that high school students and counsellors can be guided to avoid schools which are not on the accredited list. When this list is

puhlished, reports indicate that ahout 24 per cent of the schools or 276 of a total of 1,170 state approved schools of nursing will not be on the accredited list. These schools not accredited can be adversely affected, both directly and indirectly, as a result of any wide puhlicity and distribution of the list of accredited schools.

This action is being taken in spite of the overwhelming shortage of nurses; in spite of our need for more, but not fewer nurses; in spite of the fact that 38½ per cent of all state's approved schools of nursing have average enrollment of 50 students or less. Surely, the possible decrease of this significant number of students should be carefully weighed before any action which might affect small schools of nurses. It is evident that the accrediting program, as presently constituted and functioning, should be thoroughly studied and evaluated by hospital trustees, administrators, the medical profession, and the nursing profession as well as the most important, the general public. The three factors of the present organization stated purpose and emphasis of their purposes, and present practicality and objectivity of the administration should be thoroughly examined and discussed by all groups concerned. It is with humility that I present this resume of findings in regard to the nursing prohlem in the midwest and in our state. It is obvious that no one person can definitely state the solution for this problem. We have nurses now who are married and have come back to work. As you know, many of the nurses who leave hospitals within a year or two go home and get married and raise a family and there is no way known at the present time to put a stop to this and ask these girls to continue nursing care. It is my opinion that with careful study and cooperation the problem can satisfactorily be worked out.

F. E. Erenfeld, M.D., Chairman

American Medical Education Foundation

The following is my report of the American Medical Education foundation meeting in the Sheraton hotel in Chicago, Sunday, January 25, 1953:

A representative was present from about every state. Following a message of welcome, we were addressed by Dr. Donald G. Anderson, secretary-treasurer of the American Medical Education foundation, who brought us up to date on the progress being made by the National Fund for Medical Education and by the American Medical Education foundation. At this time, about $3,000,000 had been distributed among our medical schools and that amount will be markedly increased this year with the list of contributors to include medical societies, women's auxiliaries, medical publishers, individual physicians, laymen, pharmaceutical houses, insurance companies, oil companies, and industrial firms too numerous to mention. Some of these gifts from industries are contingent upon the showing the doctors themselves make.

Last year in North Dakota, twelve doctors and one layman contributed $1,005. The layman, I would like to add, was none other than our executive secretary, Lyle A. Limond. Practically the same group were the only contributors in 1951.

A state committee meeting was planned for this spring. It was not called for three reasons. First, after dividing one's earnings with the department of internal revenue, for a time at least the spirit of self-preservation exceeded the spirit of charitable giving. Two, after attending this meeting and hearing the results of various methods used, I realize we lack the organization to successfully contact the membership. It cannot be done by a single committee working on a state level. Third, such a campaign must be preceded by a program of enlightenment as far as the membership is concerned.

I would like to suggest that this committee be made up of one man from each district society, that man being recommended to the president of the state society as a man that can be depended upon to work, for his work is going to be to personally contact each member of his district scociety. This appointment should be made in July and a meeting of the entire committee held early in September. During the summer months, material must reach the hands of each and every member of the association that he may be thoroughly familiarized with the need and purpose of this program.

Oftentimes we resent being told what we should give. This will not be done. If we can only get across to the individual doctor the needs of his school and revive in him a little of his old school spirit, I know there will be few donations less than $100, which represents but $.22 a day and if you take the federal tax into consideration, you can cut that in two.

Gentlemen, we are faced with a real need—a responsibility that we can ill afford to neglect, a duty each and everyone of us must face up to. Let's make a showing worthy of the state from which we come and make a showing at the next national meeting of which we can be justly proud.

W. E. G. Lancaster, M.D., Chairman

Medical Economics

Your committee on medical economics met twice during the past year with 90 per cent attendance by the members.

The fall meeting was held Sunday, November 2, 1952, at our state office in Bismarck, and the following items were considered:

Mr. Campbell and Mr. Ellis of the Franklin Life Insurance company presented aspects of a special retirement plan which is written individually and has no group requirement. This was tabled by the committee since it was felt that no stamp of approval he given any insurance carrier offering retirement plans.

The welfare board fee schedule problem was again brought up for discussion and the consensus of the members present was that this problem should remain on the county level at least for the time being. This then remains in the same status as was reported for the past two years. There is no welfare board fee schedule in effect, as our proposed schedule which was adopted by this committee several years ago was not adopted by the state welfare board. It is therefore necessary for the physicians in the different localities to come to a satisfactory understauding with their local welfare boards, and from reports thorughout the state, this is being done. We therefore recommend discretion and fairness in the fees charged to the local welfare boards to make this plan work as we hope it should.

Negotiations have been completed with the bureau of Indian affairs for the plan whereby the doctors would take care of indigent Indians at similar fees to those we had offered to our state welfare board. This plan is now in effect and all indigent Indians are entitled to care from the doctors in the state at these rates. It is the plan of the bureau of Indian affairs to close out the Indian hospitals, and when this is finally done, the entire care of indigent Indians will be up to the practicing physicians in the state.

No problems have arisen with the workmen's compensation bureau during the past year and an excellent cooperation has taken place between this bureau and the doctors in the matter of fees and treatment of these cases.

The committee spent considerable time in discussing and giving its final approval to the uniform insurance reporting form. Our executive secretary was authorized to have the forms printed and to distribute them upon receiving requests from the membership of the association. A small service charge is to be levied to cover distribution, packaging, and postage. This charge was set at $1.50 for pads of 100 and $1.25 for pads of 100 in lots of 500 or more. A copy of the insurance reporting form was sent to our association membership along with the December newsletter. It is strongly recommended by this committee that all doctors, clinics, and hospitals in the state use tbese forms so that a universal system can be established. Any further correspondence regarding these forms will come through your newsletter from our executive secretary. This form is the result of several years work by the committee and was worked in collaboration with the state federation of insurance companies. Other states have adopted this form after our inauguration of the same.

The group disability insurance program has been sold to over 50 per cent of the members and is now in full force. This program appears to afford considerable saving in disability insurance rates and any member of the North Dakota State Medical association can apply for the same. Further information can be had from our executive secretary.

The spring meeting of the committee was held Saturday and Sunday, April 11 and 12, 1953, at the Patterson hotel in Bismarck. The following items were discussed:

The field representative in North Dakota for the National Foundation for Infantile Paralysis, Inc., Mr. James Fenelon, came before the group in regard to a fee schedule for this program. After considerable discussion as to fees, county advisory medical committees to county polio chapters, hospital costs, and so forth, your committee decided against a fee schedule at this time since the relationship between the national foundation through their North Dakota field representative and the members of our association has been harmonious in the past. It was also suggested that the patient always be billed for polio cases by the doctor who attends him. Mr. Fenelon stated that to the best of his knowledge, four out of five polio patients had their bills paid by the national foundation in this state during the last year.

An x-ray fee schedule for the various clinics for the crippled children's program throughout the state was discussed and adopted. This fee schedule is to be sent out to all the hospitals that participate in the taking of x-rays for the crippled children's diagnostic clinics throughout the state. It is recommended by your committee that this schedule be adhered to when the clinics visit your town throughout the state. Due to the increased cost in taking x-rays, it was concluded that the previous fee schedule for this work has been inadequate.

Mr. William F. Little of the I. C. System of Minneapolis appeared before your committee requesting approval of the bureau which he represents in this area. He offered us a proposal whereby his company would aid the members of the North Dakota State Medical association wishing help in the collection of their accounts, for a commission of 20 per cent. However, 2 per cent of this would be paid the North Dakota State Medical association by his organization and the balance of 80 per cent would be

retained by the physician whose accounts were collected. The I. C. System of Minneapolis provides: (1) considerable advice on the collection of delinquencies, (2) additional assistance at no cost to the creditor, (3) a gentle pressure system originating in Minneapolis. This latter service consists of a series of letters, postcards, registered letters, collect telegrams, and an attorney letter—all telling the debtor to pay his account to his creditors.

naire by mail. This questionnaire was sent to 25 rural hospitals in towns of 2,500 population and under. Nineteen of these questionnaires were returned. Your chairman would like to have personally visited all these rural hospitals, but time did not permit such an investigation.

Your chairman wisbes to report the following findings from the reports of 19 rural hospitals listed in the following chart:

Town	*Who Operates Hospital*	*No. Beds*	*Patient Daily Average*	*Per cent of Occupancy*	*Daily Cost per Patient*	*No. Drs. on Staff*	*Type of Practice*
Elgin	Community	31	16.4	53%	$13.01	3	Group
Harvey	Church	40	27.9	69	12.65	6	Independent
McVille	Community	13	5.7	44	13.00	1	Independent
Bowman	Church	20	8.6	31		1	Independent
Moball	Church	26				2	Group
Crosby	Church	33	10.2	31	12.00	2	Independent
New Rockford	Church	38	21.1	55	7.50	3	Independent
Oakes	Church	17				4	Independent
Northwood	Church	25	14.4	57	9.86	5	Independent
Cooperstown	Community	28	13.6	49	15.80	3	Group
Drayton	Church	14	12.3	89	8.83	1	Independent
Mayville	Community	31	13.9	45		5	Independent
Garrison	Church	28				2	Independent
Carrington	Church	25	12.1	48		2	Independent
Hazen	Church	30	20	66	13.20	3	1–Independent 2–Group
Langdon	Church	35	20.8	59		3	1–Independent 2–Group
Rolla	Church	24				2	Independent
Powers Lake	Community	13	6.	46	8.00	1	Independent
Kenmare	Church	33	17.7	54	10.00	2	Group

The cost seems reasonable—$1.00 per account plus 20 per cent of amount collected. Letters to your debtors will go out under the title of the Professional Credit Protective Bureau. The stationery, postage, and the work will be provided by the I. C. System. Physicians using this service will handle all money and all settlements. Mr. Little stated that in no case does the I. C. System handle any money or settlements, nor do they make any personal collection, nor take any legal action whatever—it being considered poor policy for the creditor to let control of these vital matters out of his hands except to local legal talent. While no system of collecting accounts can be considered absolutely perfect, the I. C. System has been reported by those committee members using it as being a very satisfactory service. Our executive secretary reported that the immediate past president of the North Dakota State Dental association, R. L. Bork, D.D.S. of Bismarck, stated that his association reports favorably on the I. C. System's record under a contract with them. Your committee recommends that the house of delegates of the North Dakota State Medical association give approval to entering into a contractual agreement with the I. C. System of Minneapolis.

TED KELLER, M.D., Chairman

SUB-COMMITTEE ON MEDICAL PRE-PAYMENT PLAN

Everything in the realm of prepaid medical plans seems to be running smoothly. The Blue Shield is working on plans to iron out minor inequalities in their fee schedules. A meeting will be held at the time of the state meeting. Any member of the Blue Shield who has a grievance will be heard.

The sub-committee as such held no formal meeting this year. Members of the committee sat in with the economics committee and heard discussions relative to a uniform insurance reporting form. The committee went on record approving the form submitted by the various underwriters. However, a lot of difficulties have arisen and further study and plans have to be made before a uniform form can be used. In the interim, the committee recommends the form approved by the North Dakota State Medical association. If everyone used this form, minor adjustments could be made when necessary.

O. A. SEDLAK, M.D., Chairman

SUB-COMMITTEE ON RURAL HEALTH

Your committee on rural health respectfully submits the following report:

Your chairman was unable to attend the national conference on rural health held at Roanoke, Virginia, this past February. Dr. Willard Wright from Williston attended this meeting and he informed the chairman that it was a very good meeting and was well attended.

Your committee on rural health held a meeting at Rugby, March 25, 1953. Two members of your committee were present. Also attending was our state president, Dr. O. W. Johnson; Lyle A. Limond, executive secretary of the North Dakota State Medical association, and Mr. Arne G. Bjorke, administrator of the Good Samaritan hospital at Rugby.

A survey of hospitals and health facilities in rural areas in North Dakota was carried out by sending out a survey question-

Your chairman wishes to submit a brief analysis of the hospital survey:

10 hospitals are operated by the Catholic Sisters.
4 hospitals are operated by Protestant groups.
5 hospitals are community type hospitals.

There are 504 beds reported by the 19 hospitals. Serving these hospitals are 51 doctors—9.9 beds per doctor.

There are 6 areas where the doctors practice as a group. In all the other areas the doctors practice independently.

Fifteen of the hospitals reported their daily patient census. Five of these hospitals are operated with less than 50 per cent occupancy, and ten hospitals are operated with over 50 per cent occupancy.

Eleven hospitals reported their daily cost per patient. This daily cost varied from $7.50 per day to $15 per day. The average daily patient cost was $11.26 per day.

All the hospitals, except one, reported their income was sufficient to meet operation costs.

Four hospitals reported a detailed operation financial statement. Some of these hospitals could not give a financial statement because they had only been operating three to four months.

All the hospitals use practical nurses and nurses' aids. The wages varied some. The included wage schedule is fairly correct.

Superintendent nurses	$275 to $300 plus maintenance
Regular registered nurses	180 to 250 plus maintenance
Practical nurses	125 to 175 plus maintenance
Nurses Aids, full time	80 to 125 plus maintenance
Nurses Aids, part time	40 cents to 60 cents per hour

All the hospitals, except one, were using nurses aids, and they all reported that the nurses aids were working out satisfactorily.

One superintendent included this comment, and your chairman quotes: "Since the opening of our hospital we have had to employ more nurses aids for bedside care than registered or practical nurses. We have not done this because we so desired, but because we had no alternative. The majority of the high school graduates whom we employed were not sure nursing was their prime interest and felt that a nurses aid position might be a way of confirming this. In several cases, these girls had the ability and interest, but the majority were of the type who were too immature; then too, many were financially unable to enter nurses training. A number of these girls would have become fine nurses.

To obtain satisfactory care for both the patient and to uphold the reputation of the hospital with nurses aids is utterly impossible

One or two trained nurses in a small hospital cannot hope to give them the background in a few weeks or months that the nurse herself gets during her entire period of training. Just about the time a nurses aid has become well oriented to fulfilling what is expected of her, she becomes restless and decides to see if the grass isn't a bit greener elsewhere. Consequently, the turnover is too great to be of any benefit to either the patient or the institution.

In the not too distant future, if at all possible, we hope to employ only registered and practical nurses because on the whole,

they are more stable and have already learned what is expected of them."

Since 1948, 19 new hospitals have been built and are in operation in the rural areas. Thirteen of these hospitals had federal aid. Twelve more hospitals are under construction in the various rural areas. Three of them are using federal aid.

General hospital beds in North Dakota, in operation (Based on 1953 license application)	3,121
Under construction or at standstill	250
Total	3,371
Population of North Dakota (1950 census)	619,636
Present beds per 1,000 population	5 per thousand
Beds per 1,000 population when beds under construction are completed	5.4 per thousand

The rural health committee took part in the program with the public health association meeting held at Grand Forks, October 10, 1952. This was a panel type of program and the discussants and topics are listed.

Dr. W. A. Wright, Williston, moderator.

Dr. O. W. Johnson, Rugby, president, state medical society—Greetings from state medical society, and comments.

Mr. Aubrey Gates, guest speaker, introduced by Dr. W. A. Wright, speaker, to choose own topic.

Mr. Lyle A. Limond, executive secretary, state medical association—Public relations with the radio and the news.

Dr. D. J. Halliday, Kenmare—Problems in hiring and training nurses for the rural hospitals.

Mr. G. A. Ruana, Elgin—Business manager from the Lorenzen Memorial hospital—Administration problems in the rural hospital.

Miss Ilah Wibe, Elgin, North Dakota public health nurse in the Custer district health unit—Public health in the rural areas.

Mr. Ralph Beede, Elgin, attorney and editor—The rural doctor, the rural hospital, and the news.

Dr. T. Stangbye, Mott—Dental education in rural dentistry.

Mrs. Richard Werre, Elgin, R.N., superintendent of nurses, Lorenzen Memorial hospital—The rural hospital superintendent.

Mr. Arnold Goplen, Bismarck (North Dakota state department of health, division of hospitals)—The Hill-Burton program.

Dr. M. S. Jacobson, Elgin—Remarks, 15 years in a general practice.

Mr. Aubrey Gates is the field director on rural health for the A.M.A. He is an interesting and inspiring speaker. Mr. Gates was the speaker for the evening banquet. His topic was "To Each His Own." Your chairman wishes to thank Dr. W. Wright of Williston for obtaining such an able speaker for us. Your chairman also had the opportunity of spending several hours with Mr. Gates discussing many rural problems. Mr. Gates has traveled in all our states and has a very comprehensive knowledge of our rural health problems.

The public health association has extended our committee an invitation to participate in their program again this year. The meeting is to be held in Dickinson, October 26 and 27.

Your chairman wishes to make the following recommendations:

1. That our committee continue the survey of rural hospitals and rural health facilities for at least two more years. So far the survey has cost very little money, probably $25.00.

2. That our committee also have one representative from the hospital division of the North Dakota state health department and one member from the North Dakota State Hospital association.

3. That our committee continue to take part in the program of the North Dakota Public Health association. Your chairman urges more publicity be used to encourage more rural people to attend the meeting.

M. S. Jacobson, M.D., Chairman

SUB-COMMITTEE ON VETERANS MEDICAL SERVICE

The following is a report of the chairman of the sub-committee on veterans medical service to the committee on medical economics and to the house of delegates.

The veterans medical service division of the North Dakota State Medical association has been in operation for seven years.

The office continues to be on what we call a "cash basis," meaning that the monthly expenses are reimbursed in full by the Veterans' administration.

The office still has a loan of $2,500 from the state medical association, but this is solvent in the sense that it is equalled by funds in the bank account which is required as a circulating fund for the office and also in the possession of furniture and fixtures in the office.

The total amount of fees transmitted by this office to doctors in North Dakota in 1952 was $28,919.50. The average total of each authorized examination was $14.80. The greatest difficulty in actual administration and greatest annoyance to the participating physicians is the requirement that the certification on each authorization be signed (this refers to the certification that the fee charged for the service rendered is no greater than the fee rendered nonveterans for the same care). We have attempted to explain by circulars, letters, and personal interviews that this is a government requirement and we have no choice in the matter but to insist that it be followed.

Likewise, our request that the fee charged by the doctor be sent in to the office is a reasonable one as the administrative staff must know the exact charge which was placed.

Mrs. Anita Meisner continues to operate the office efficiently. Our relationship with the Veterans' administration continues to be cordial and satisfactory.

The committee recommends the continued operation of the plan as it is in effect at the present time and asks the continued cooperation of the physicians participating in the plan.

R. B. Radl, M.D., Chairman

NEW BUSINESS

Dr. Spear asked for comment on the first order of business which was to set the per capita dues for the ensuing year, inasmuch as it is the custom to have this decided on the floor of the house of delegates. Considerable discussion followed on the matter, and it was agreed to table it until after the second meeting of the council.

The next order of business was the appointment of a nominating committee by the president, Dr. O. W. Johnson. The names of the nominating committee were read by Dr. Boerth, secretary, and are as follows: Dr. C. J. Glaspel, chairman, and Drs. A. R. Gilsdorf and Tom Pederson.

Speaker Spear next asked to have an announcement from the various chairmen of the reference committees as to the time and place of the committee meetings, and asked for any supplementary reports that any committee wished to bring up at this time.

Dr. Erenfeld, chairman of the committee on nursing education made the following supplementary report:

"We would like to have the association appoint two of its members to a midwest committee on improvement in the care of patients. This committee is made up of members of the medical profession, the nursing association, league of nurses, and the hospital association of fifteen midwestern states. The aims of this committee are to promote better patient care and a closer association in the member states, especially regarding nursing care. These two doctors to be appointed by the association would be liaison members to this committee."

Speaker Spear requested that Dr. Erenfeld meet with Dr. Youngs, the chairman of the reference committee for standing committees.

Dr. Youngs asked for the floor at this time and informed the house that he had been requested by the North Dakota Speech and Hearing council to ask the North Dakota State Medical association to approve in principle a program which they wish to institute to detect speech and hearing difficulties in school children, and to refer these handicapped children for proper medical attention, and then to further refer those that cannot be helped by medical means for proper hearing aids, lip reading or other corrective measures indicated. The council asked that the medical association appoint a member to act in an advisory capacity to this council.

Speaker Spear referred this matter to the proper committee.

The next item to be referred to the proper committee for a recommendation was the matter of a physician placement service. This would be in the hands of the executive secretary's office and would work in close liaison with the state board of medical examiners. There is a definite need of a placement service to get doctors to the towns urgently needing them, and also to help place doctors requesting a location in North Dakota. A report on this would be given at the second meeting of the house.

Adjournment

It was moved and seconded that the first session of the house of delegates adjourn to reconvene at 2:00 p.m., Sunday afternoon.

SECOND SESSION, HOUSE OF DELEGATES

Sunday Afternoon, May 10, 1953

Minot, North Dakota

The second session of the house of delegates was called to order at 2:30 p.m., May 10, 1953, in the dining room of the YMCA building, Minot, North Dakota.

Dr. Haugrud, chairman of the credentials committee, reported that there was a quorum present. The following doctors answered the roll call:

G. W. Toomey, Devils Lake; C. V. Bateman, Wahpeton; E. M. Haugrud, Fargo; Nelson Youngs, Grand Forks; C. M. Graham, Grand Forks; R. E. Mahowald, alternate, Grand Forks; J. D. Craven, Williston; A. R. Sorenson, Minot; D. J. Halliday, Kenmare; A. F. Hammargren, alternate, Harvey; W. Gilsdorf, Valley City; R. O. Saxvik, Bismarck; R. B. Radl, Bismarck; R. W. Rodgers, Dickinson; Tom Pederson, Jamestown; K. G. Vandergon, Portland.

The reading of the minutes of the first session was dispensed with upon motion of Dr. Gilsdorf, seconded by Dr. Youngs.

The regular order of business was put aside at this time and Dr. Radl was asked to report on the placement service discussed during the first session, in order that the matter might be referred to the council.

Dr. Radl reported as follows:

"It is recommended that the North Dakota State Medical association include in its activities a professional placement service. The purpose thereof is to serve as a central agency through which may be cleared information and requests by physicians seeking locations in the state. It would serve also to assist communities, physicians, and hospitals which may be seeking physicians, residents, and interns.

It is suggested that this agency work in liaison with the state board of medical examiners and the state selective service advisory committee; both of these receive information currently regarding physicians who may be interested in locations in the state.

It is hoped that this program can be instituted in the immediate future.

Signed: R. B. Radl, M.D., chairman; C. M. Graham, M.D., D. J. Halliday, M.D., W. R. Fox, M.D."

It was moved by Dr. Mahowald that this report be adopted and that the motion be passed on to the council. The motion was seconded by Dr. Graham.

Dr. Spear, speaker of the house, informed the house of delegates that with their approval, the council next had to act on the recommendation and if it met with their approval, the executive secretary would then carry it out.

Selection of 1953 Meeting Place

Dr. Youngs extended the house an invitation from both the president of the Grand Forks District medical society and the secretary of the chamber of commerce of Grand Forks to meet in Grand Forks in 1954, and offered full cooperation. This motion was seconded by Dr. Gilsdorf and unanimously passed.

The Speaker next appointed a committee consisting of Drs. Halliday, Youngs, and Gilsdorf, to consider the invitation extended the North Dakota State Medical association by the South Dakota State Medical association to hold a joint meeting with them in 1956 at the time of their 75th annual meeting. Their report will be given to the house of delegates at the time of the annual meeting in Grand Forks in 1954.

REPORT OF NOMINATING COMMITTEE

Election of Officers

Dr. Glaspel, chairman of the nominating committee, presented the following report:

President	JOSEPH SORKNESS, Jamestown
President-elect	P. H. WOUTAT, Grand Forks
First vice-president	D. J. HALLIDAY, Kenmare
Second vice-president	R. H. WALDSCHMIDT, Bismarck
Speaker of the house	G. A. DODDS, Fargo
Vice-speaker of the house	R. E. LEIGH, Grand Forks
Secretary	E. H. BOERTH, Bismarck
Treasurer	E. J. LARSON, Jamestown
Delegate to the A.M.A.	W. A. WRIGHT, Williston
Alternate delegate to A.M.A.	G. W. TOOMEY, Devils Lake

COUNCILLORS:

Terms expiring 1954:

Fourth district	A. D. McCANNEL, Minot
Fifth district	C. J. MEREDITH, Valley City

Terms expiring 1955:

Second district	J. C. FAWCETT, Devils Lake
Seventh district	R. D. NIERLING, Jamestown
Ninth district	A. R. GILSDORF, Dickinson

Terms expiring 1956:

First district	O. A. SEDLAK, Fargo
Third district	NELSON YOUNGS, Grand Forks
Sixth district	R. B. RADL, Bismarck

Board of Medical Examiners:

H. L. REICHERT	Dickinson
O. W. JOHNSON	Rugby
JOSEPH SORKNESS	Jamestown

Member, Medical Advisory Board:

L. W. LARSON	Bismarck

Member, State Health Council:

O. W. JOHNSON	Rugby

The Speaker announced that a motion would be in order to declare the nominees duly elected to their respective offices. On motion made and seconded that the nominees be elected unanimously, all voted aye and the above officers were elected unanimously.

At the 1952 annual meeting, held in Fargo, the house of delegates carried the motion that the annual meeting be held the second Saturday in May. Due to the fact that this generally falls on the Mother's day week-end, the motion was made by Dr. Gilsdorf and seconded by Dr. Vandergon that the motion of 1952 be reconsidered and that the time of the annual meeting be set for the first Saturday and Sunday in May.

REPORTS OF REFERENCE COMMITTEES

Reference Committee to Consider the Report of the President, Secretary and Special Committees

Dr. Youngs, chairman, presented the following reports and their discussions, which were adopted section by section, and as a whole.

1. *Report of the President.* The reference committee has considered the report of the president with special note of the large amount of work done by him in the interest of the association. We wish to take this opportunity to express our thanks for a job well done.

We note the president recommends a "grass root" organization of "on the spot" members for the purpose of contacting legislators personally, and we concur with this thought and recommend that such an organization be implemented by our legislative committee.

We note the failure of some committees to function. We consider this situation deplorable, but the association is financially unable to foot the bill for such meetings. We feel this failure stems from two sources; namely, lack of interest and lack of subject.

This portion of the report was adopted and the speaker reminded the house that it will be up to the new president and the executive secretary to put the above into effect. Motion carried.

Dr. Youngs brought to the attention of the house the recommendation to set up a "mileage and per diem committee" for the president. Since the finances of the association will not stand any large annual outlay of funds, it was recommended to the council that $200 annually be placed at the disposal of the president to use as he sees fit to defray the expenses of his office. It was further recommended that the president call on other officers of the association to represent him in any official capacity whenever feasible.

This portion of the report was unanimously adopted.

Considerable discussion followed Dr. Youngs' reviewal

of the president's suggestion for the development of an executive body consisting of the state officers with top officers of each district society, and it was recommended that this be implemented and that the president be called upon for concrete suggestions of ways and means to institute this program.

Dr. Youngs moved that an amendment be made to the constitution and by-laws, article VI, section 4, whereby "A majority of members of the council shall constitute a quorum for the transaction of business," instead of the number "six."

He also moved that the speaker appoint a committee of three to study the possibility of changing the constitution and by-laws, so as to either have an executive body consisting of state officers and the top officers of each district, or have the council remain in its same capacity with the addition of alternates for each district to act in case the councillors cannot function.

This was seconded by Dr. Rodgers and the motion carried.

The speaker appointed Dr. Youngs, chairman, Dr. Radl and Dr. Sorenson to this committee.

2. *Report of the Secretary.* The reference committee reviewed the report of the secretary, Dr. Boerth, and commended him for a job well done. This portion of the report was adopted.

3. *Report of the Executive Secretary.* The reference committee reviewed the excellent detailed report of the executive secretary, and recommends that each member of the association read this report in its entirety.

The committee is in complete accord with recommendations regarding medical-press-radio conferences, rural health committee's small hospital survey, continuation of the inter-professional liaison committee and the suggestion regarding the committee on scientific program. Thought should be given to a committee on constitutional revision to consider this suggestion. This portion of the report was adopted.

The committee concurred with the suggestion that medical doctors on the medical school faculty at the university become full-fledged dues-paying members of the district and state association. This portion of the report was adopted.

The committe recommended that the medical-press-radio code be adopted. It was recommended that the president of the North Dakota State Medical association send congratulatory telegrams and letters to Mr. T. Manley Brist, legal counsel for the Minnesota State Medical association. This portion of the report was adopted.

4. *Special Committee on Emergency Medical Service.* The reference committee reviewed the report of the committee on emergency medical service and note improved relationship in Red Cross blood donor program. This portion of the report was adopted.

5. *Committee on Industrial Health.* The committee had no recommendations to make. This portion of the report was adopted.

6. *Committee on Mental Hygiene.* The committee recommends that follow-up letters be sent to referring medical doctors.

They agreed with the recommendation that nurses should receive psychiatric training in the state of North Dakota at the Jamestown state hospital.

It was recommended that the North Dakota State Medical association become a life member of the North Dakota Mental Health association, and pay the $50 membership dues. They also concurred with the other three recommendations of this committee; namely, that efforts should be made to influence authorities to change the name from "county insanity board," to "county board of mental health," and that the state medical association should support psychiatric clinics which are being planned; and the recommendations for the rehabilitation of patients at Jamestown state hospital be considered and that a plan of placing such patients in industry outside the state be developed. This portion of the report was adopted.

7. *Sub-Committee on Mental Health.* The committee noted the lack of medical treatment for acute alcoholics at the state lodge. They concurred with the committee that the alcoholics program should share proportionately in the welfare funds collected through the state sales tax. This portion of the report was adopted.

8. *Committee on Displaced Physicians.* The committee noted that the D.P. program is closed at present and that no displaced physicians are allowed to come into North Dakota at the present time with the exception of a limited number who will be allowed to practice in various state institutions. This portion of the report was adopted.

9. *Committee on Diabetes.* The committee notes the lack of response in local detection drives during the past year and also noted that the committee is considering a new approach to rekindle enthusiasm through the use of Dreypak as a means of detection. This portion of the report was adopted.

10. *Committee on Nursing Education.* The committee found this to be an excellent, detailed report and should be read by each member of the association. It recommended that the state association go on record as approving the principle of a midwest committee on improvement in the care of patients, made up of members of the medical profession, nursing association, league of nurses, and hospital association, of 15 midwestern states. The aims of this committee are to promote better patient care and a closer association in the member states, especially regarding nursing care. The committee further recommended that two doctors from the association be appointed as liaison members to this committee. This portion of the report was adopted.

Speaker Spear informed the house that the two members of the association to act as members of this committee would be appointed by the incoming president.

11. *Committee on A.M.A. Educational Foundation.* The committee noted the increased list of contributors and that last year 12 doctors and 1 layman contributed to this fund. It was recommended that the president of each district medical society appoint a man to contact each member of his district society to obtain contributions to this fund. This portion of the report was adopted.

The reference committee considered the request of the North Dakota speech and hearing council, and recommended that their program be approved in principle and a member of this association be appointed by the president to act as an advisor to this North Dakota speech and hearing council. This portion of the report was adopted.

The motion was made by Dr. Youngs and seconded by Dr. Vandergon that the report as a whole be adopted. Motion carried.

Nelson Youngs, M.D., Chairman
R. W. Rodgers, M.D.
K. G. Vandergon, M.D.

Reference Committee to Consider the Reports of the Council, Councillors, Delegate to the A.M.A., and Member of the Medical Center Advisory Council

Dr. W. H. Gilsdorf, chairman, presented the following report which was adopted section by section and as a whole:

1. *Report of the Chairman of the Council.* The reference committee reviewed the report of the chairman of the council and finds that a great deal of work has been done. The committee views with pleasure the administration of the $500 scholarship fund for medical students at the University of North Dakota, and very strongly recommends the continuation of the scholarship fund under its present excellent equitable administration. This portion of the report was adopted.

2. *Reports of the Councillors of the eight districts.* It was with a great deal of pleasure that the committee noted the large number of outstanding papers and discussions held in each district during the past year. All of the districts were commended. This portion of the report was adopted.

3. *Report of the Delegate to the American Medical Association.* The committee reviewed the annual report and complimented the delegate, Dr. W. A. Wright, on the large amount of work done and time expended on his part for the interests of the state association. The presentation of his factual report of A.M.A. reaction to the activities of the Magnuson commission, and the report in general, is to be particularly commended.

The committee reviewed the report of the A.M.A. delegate concerning the following problems: (1) doctors draft legislation, (2) care of veterans with non-service-connected disability in veterans hospitals, (3) the continuation of voluntary health insurance, (4) current unfavorable publicity emanating from the college of surgeons through its director, Dr. Paul Hawley.

The committee commended the delegate on his concise and clear resume of these problems. Your committee wishes to commend the delegate on his entire report and agrees wholeheartedly with the final paragraph of the report, namely: "For the first time in over 20 years, we now have an administration in Washington, pledged to good government and one which is desirous of cooperating with, and having the cooperation of the organized medical profession. This gives us a tremendous opportunity to proceed with constructive programs and to make our influence a power for good in the affairs of the nation. Greedy and unethical practices by individual physicians are the main factors which will dilute and diminish this opportunity for service to the country as a whole." This portion of the report was adopted.

4. *Report of Member of the Medical Center Advisory Council.* The committee reviewed the report of Dr. L. W. Larson and found the excellence of his report to be outstanding. Dr. Larson brought out vividly the inability of the advisory council to overcome public influence and political pressure along with lack of cooperation on the part of the university administration. This portion of the report was adopted.

The reference committee recommended that the chairmen of the various committees have their reports into the office of the executive secretary one month previous to the state meeting, making it possible for the handbooks to be in the hands of the delegates two weeks before the meeting so that the contents of the report may be studied. This portion of the report was adopted.

The motion was made by Dr. Gilsdorf and seconded by Dr. Halliday that the report as a whole be adopted.

W. H. Gilsdorf, M.D., Chairman
C. V. Bateman, M.D.
R. E. Mahowald, M.D.
A. F. Hammargren, M.D.

Reference Committee to Consider Reports of the Standing Committees Except the Report of the Committee on Medical Economics and Its Sub-Committees

1. *Report of the Committee on Official Publication.* The committee reviewed the report of the committee and recommended that the Journal-Lancet be continued as the official publication for the coming year. This portion of the report was adopted.

2. *Report of the Committee on Crippled Children.* The committee commended the work which has been done in the past year, particularly in revamping the outmoded fee schedule, and for their insistence that crippled children services be rendered in the state when such services are available. This portion of the report was adopted.

3. *Report of the Committee on Necrology and Medical History.* The committee noted with a feeling of deep sadness and regret the passing of 8 members in the past year, several of whom held prominent offices in the organization and rendered great service to the progress of medicine in North Dakota. They are as follows:

Paul H. Burton, former association president; J. E. Countryman, former association president; James A. Hanna, former association president; Jacob H. Fjelde; George Emerson Heinzeroth; George R. Waldren; Elizabeth P. Rindlaub; Milo H. Culbert.

This report was followed by the house of delegates standing for a moment of silence with reverence and respect to these members who have passed away this past year. This adopts this portion of the report.

4. *Report of the Committee on Public Health.* The committee commended the activities of the public health committee during the past year and wished to place special emphasis on the recommendation of the committee on public health that the state medical association notify the bureau of Indian affairs to intensify its case-finding practices on the several Indian reservations. They recommended that the executive secretary be authorized to transmit the recommendation on tuberculosis to Fred G. Aandahl, assistant secretary of the Department of the Interior, Washington, D. C.

The reference committee also voiced their appreciation to the state health department for information as to the availability of gamma globulin in the prevention of poliomyelitis. This portion of the report was adopted.

5. *Report of the Committee on Medical Education.* The committee carefully reviewed the report of the committee on medical education, which contained controversial issues relevant to the establishment of a four-year medical school. This move is of vital concern, not only to the physicians of the state, but to all of its citizens. This portion of the report was adopted.

6. *Report of the Committee on Fractures.* This report was reviewed and adopted.

7. *Report of the Committee on Maternal and Child Welfare.* This report was reviewed and adopted.

8. *Report of the Committee on Cancer.* This report was reviewed and the education program sponsored by

the North Dakota Cancer society was found especially noteworthy. This portion of the report was adopted.

9. *Report of the Committee on Public Policy.* This report was reviewed and the suggestion made that the chairman of the committee, Dr. O. A. Sedlak, discuss and further explain his proposed change for the committee of public policy and legislation before the house of delegates. This portion of the report was adopted.

Dr. Sedlak spoke regarding the proposed change, as follows: "This has been discussed previously, whereby members are appointed from each one of the 49 legislative districts so that we have a closer liaison with our representatives in Bismarck at the time the legislature meets. I think that program should be set up by the new president." This report as a whole was adopted.

A. R. Sorenson, M.D., Chairman
Tom Pederson, M.D.
J. D. Craven, M.D.

Reference Committee to Consider the Reports of the Committee on Medical Economics and Sub-Committee on Prepayment Medical Care, Veterans Medical Service and Rural Health

Dr. R. B. Radl, chairman, presented the following report, which was adopted section by section and as a whole:

1. *Report of the Committee on Medical Economics.* The committee reviewed this report as printed in the handbook, and the following recommendations were made concerning the report:

The Franklin Life Insurance company presented aspects of a "special retirement plan." The committee on medical economics felt that no stamp of approval should be given any one insurance carrier offering retirement plans. Your reference committee approved their action. This portion of the report was adopted.

The committee noted that the welfare board fee schedule was a problem that should be left as at present; namely, an understanding between the respective county officials—county welfare boards, and the local physicians. This committee does not agree to this method of doing business. The welfare board of North Dakota is an agency and their financial responsibility for medical care should be the same in all counties in the state. So, too, should be the method of handling these clients; namely, free choice of physician by the individual. The committee regrets to say that the state welfare board does not hesitate to place before the public the high cost of indigent care on the medical doorstep. It would be the recommendation of the reference committee that the committee on economics conclude a concrete agreement on a state-wide basis with this agency. This portion of the report was adopted.

The committee further noted whereby a plan has been put into effect with the bureau of Indian affairs, whereby the doctors would care for indigent Indians on the same fee schedule as that offered to our state welfare board. The reference committee recommended approval of this plan. This portion of the report was adopted.

The committee on medical economics found no problems arising with the workmen's compensation bureau during the past year, and the reference committe recommended approval of the report. This portion of the report was adopted.

It was recommended by the reference committee that all doctors, clinics, and hospitals in the state use the uniform insurance reporting forms as approved by the committee on medical economics, in order to establish a uniform system. The reference committee feels that the committee on medical economics is to be commended for their excellent work in developing these forms and recommends their approval. This portion of the report was adopted.

The committee on medical economics recommended that no definite fee schedule be set up for the polio program initiated by the National Foundation for Infantile Paralysis, since the relationship between the national foundation and the members of our association has been harmonious in the past. It was also suggested that the patient always be billed for polio cases by the doctor who attends him. The reference committee recommended approval of this report. This portion of the report was adopted.

The reference committee recommended that the new x-ray fee schedule as set up by the committee on medical economics for the various clinics for the crippled children's program be adopted and used by all x-ray departments throughout the state. This portion of the report was adopted.

The committee on medical economics met with Mr. W. F. Little of the I. C. System of Minneapolis, who offered a proposal whereby his company would aid the members of the North Dakota State Medical association wishing help in the collection of their accounts.

The committee on medical economics recommended that the house of delegates of the North Dakota State Medical association give approval to entering into a contractual agreement with the I. C. System of Minneapolis. The reference committee felt that the house of delegates should not enter into any contractual agreements placing their stamp of approval on any one commercial concern. In making this recommendation the reference committe in no way criticized the I. C. System of Minneapolis as a plan for collecting accounts. For the reasons given, the reference committee recommended that this portion of the report be not approved. This portion of the report was adopted.

It was moved by Dr. Radl, seconded by Dr. Gilsdorf, that the report of the committee on medical economics be adopted section by section and as a whole. Motion carried.

2. *Report of the Sub-Committee on Prepayment Medical Care.* It was the opinion of the reference committee that the report of the sub-committee on medical prepayment plans be approved. It appears from the report that the Blue Shield plan has been working very smoothly and minor adjustments in the fee schedule are being planned to make up for some inequalities in their fees. This portion of the report was adopted.

3. *Report of the Committee on Veterans Medical Service.* The reference committee reviewed the report of the committee and noted that the office continues to be on a "cash basis" and that the total amount of fees transmitted by this office to the doctors in North Dakota in 1952 was $28,919.50, which was a decrease from the previous year in spite of a shortage of veterans administration physicians. The committee recommended the continued operation of the plan as it is in effect at the present time, and asks the continued cooperation of physicians participating in the plan. This portion of the report was adopted.

4. *Report of the Committee on Rural Health.* The reference committee thoroughly reviewed this report and commended Dr. Jacobson for his untiring efforts in assembling such an enlightening report. This report rather completely deals with the rural hospital facilities in 19 of the 25 communities of under 2,500 population. There

are 504 beds available for occupancy and only 221 are being used and there are 51 doctors to administer to their needs. This report very rightly implies the inadequacy of the nursing care available in these rural hospitals.

The reference committee concurred that a further survey of rural hospitals and rural health facilities be continued but did not agree that this committee should include a representative from the hospital division of the state health department and one member from the state hospital association, because it was felt that information from those two organizations should be readily available upon request. This portion of the report was adopted.

It was moved by Dr. Radl and seconded by Dr. Craven that the report be adopted as a whole. Motion carried.

R. B. Radl, M.D., Chairman
C. M. Graham, M.D.
D. J. Halliday, M.D.

Reference Committee on Resolutions

Dr. R. O. Saxvik presented the following report which was adopted section by section and as a whole:

RESOLUTION

Whereas, the 66th annual meeting of the association being held in the city of Minot has received the courteous and friendly convenience and cooperation which is traditional to this city;

And whereas, the mayor, the Minot chamber of commerce, the several hotels, and others of Minot have actively assisted in making this session both enjoyable and successful;

Now, therefore, be it resolved, that the house of delegates of the North Dakota State Medical association do express their sincere appreciation by directing a copy of this resolution to the mayor of the city of Minot.

RESOLUTION

Whereas, the Woman's Auxiliary have added noteworthy contributions to their community and to their state, and,

Whereas, their gracious efforts frequently are not properly acknowledged nor acclaimed,

Now, therefore, be it resolved, that the medical association applaud the Woman's Auxiliary with their gracious president, Mrs. Esther Thorgrimsen of Grand Forks, for their support in promoting a better public understanding of the profession, as well as for their special projects for the university medical students, and for the San Haven sanatorium.

RESOLUTION

Whereas, it is the announced intention of the department of health education and welfare to support legislation which will have the effect of forcing self-employed persons into the Social Security system, and

Whereas, the vast majority of members of the A.M.A. do not desire to be taxed for the purpose, and

Whereas, we have in the past registered our disapproval of this proposal,

Now, therefore, be it resolved, that the house of delegates of the North Dakota State Medical association reaffirm its faith in the responsibility of the individual to make proper provision for himself and record their opposition to compulsory participation in the Social Security system by physicians, and

Be it further resolved, that the delegate from North Dakota to the house of delegates of the American Medical association be instructed to present this resolution for their consideration at the next meeting.

RESOLUTION

Whereas, the last volume of History of North Dakota Medicine was prepared and published by Dr. James Grassick in 1926, and

Whereas, it is desirable to compile medical history from time to time,

Now, therefore, be it resolved, that the councillors consider the commissioning of an editor to compile and publish the medical records of the state of North Dakota from 1926 to the present date.

RESOLUTION

Whereas, there has been a demonstrated need to establish a medical-press-radio code in North Dakota, and

Whereas, several states have effectively developed and used a medical-press-radio code, and

Whereas, the Devils Lake District society as well as many other individuals have urged the passage of such a code to strengthen our relationship with the public through the press and radio,

Now, therefore, be it resolved, that the state association adopt a medical-press-radio code similar to that now used in South Dakota.

RESOLUTION

Whereas, the 66th annual meeting of the North Dakota State Medical association has been presented with a most notable and educational scientific program, as well as a most refreshing entertainment schedule, and

Whereas, the Northwest District medical society, Dr. Martin P. Conroy, Minot, general chairman, and others on the several program and entertainment committees served so well to insure us of this most creditable annual meeting,

Now, therefore, be it resolved, that the house of delegates, by a rising vote of thanks, signify their gratitude and appreciation.

All the members of the house rose for this final vote of thanks.

All resolutions were unanimously passed by the house of delegates.

At this time, the speaker of the house, Dr. Spear, thanked all the delegates for their attendance and for their work at this and at former sessions, commenting on the very fine work they have done.

This was the last meeting of the house of delegates at which Dr. Spear will preside as speaker, and Dr. Halliday asked all the members to give a rising vote of thanks to him for his faithful service.

The motion was then made by Dr. Radl and seconded by Dr. Youngs that the session be adjourned sine die at 5:30 p.m.

SCIENTIFIC PROGRAM

Monday, May 11, 1953
YMCA, Minot, North Dakota

8:30 to 9:30 a.m.—Registration.

9:30 to 10:00—"Recent advances in polio therapy"—Kenneth Landauer, M.D., New York.

10:00 to 10:30—"Physiologic principles governing the regulation of electrolyte and fluid balance"—K. G. Wakim, M.D., Mayo Clinic, Rochester, Minn.

10:30 to 11:00—Intermission.

11:00 to 11:30—"Facial injuries"—Jerome H. Hilger, M.D., St. Paul, Minn.

11:30 to 12:00—"Diagnostic roentgenology in obstetrics"—George D. Davis, M.D., Mayo Clinic, Rochester, Minn.

1:30 to 2:00 p.m.—"You and the Doctors' draft"—Lt. Colonel Matthew Stockson, Hq. Fifth Army, Chicago.

2:00 to 2:30—"Congenital heart surgery"—Richard L. Varco, M.D., Minneapolis, Minn.

2:30 to 3:00—"Carcinoma of the cervix—a review of recent trends and results"—Willis Brown, M.D., University of Arkansas, Little Rock, Arkansas.

3:00 to 3:30—Intermission.

3:30 to 5:00—Panel discussion: "The acute abdomen." Moderator, Richard L. Varco, M.D., Minneapolis, Minnesota. Discussors, Willis Brown, M.D., Little Rock, Arkansas; K. G. Wakim, M.D., Rochester, Minnesota; George D. Davis, M.D., Rochester, Minnesota; Robert B. Radl, M.D., Bismarck.

Tuesday, May 12
YMCA, Minot, North Dakota

9:00 to 9:30 a.m.—"Congenital lesions of kidney, urethra and bladder," Norvel O. Brink, M.D., Bismarck.

9:30 to 10:00—"The classification and treatment of head injuries," L. A. Christopherson, M.D., Fargo.

10:00 to 10:30—"The problem of obesity"—C. F. Gasteneau, M.D., Mayo Clinic, Rochester, Minnesota.

10:30 to 11:00—Intermission.

11:00 to 11:30—"The peptic ulcer problem in infants and children"—Robert B. Tudor, M.D., Bismarck.

11:30 to 12:00—"The problem of anxiety"—Gordon R. Kamman, M.D., St. Paul, Minnesota.

2:00 p.m.—Farewell comments—O. W. Johnson, M.D., Rugby, North Dakota.

Introduction of Fifty-Year Club members and honorary members. (Dr. Johnson introduced the new members of the Fifty-Year Club of the North Dakota State Medical association to the doctors, guest speakers, and others in attendance at the scientific session.)

Members of the Fifty-Year Club in 1953 are: K. O. Knudson, M.D., Glenburn; Nels Tronnes, M.D., Fargo; Josephine Stickelherger, M.D., Oberon; Martin W. Roan, M.D., Bismarck; and J. A. Johnson, M.D., Bottineau.

Honorary members include: John G. Lamont, M.D., Grafton, and Arthur C. Morris, M.D., Fargo. Also becoming honorary members in 1953 are Dr. Stickelberger and Dr. Johnson, mentioned previously as becoming Fifty-Year Club members.

Inaugural address—Joseph Sorkness, M.D., Jamestown.

2:30 to 3:00—"Hip lesions in children"—Carroll B. Larson, M.D., University of Iowa, Iowa City, Iowa.

3:00 to 3:30—Intermission.

3:30 to 5:00—Panel discussion: "Anemias and Rh factor." Moderator, Louis Limarz, M.D., Chicago, Illinois; discussors, Robert B. Tudor, M.D., Bismarck; James D. Cardy, M.D., Grand Forks; Robert C. Painter, M.D., Grand Forks.

5:15 p.m.—Drawing for door prize.

PRESIDENTIAL ADDRESS

O. W. JOHNSON, M.D.
Rugby, North Dakota

Members of the North Dakota State Medical association, may I take this opportunity to thank one and all that have assisted me in my endeavors in behalf of your association this past year. May I again thank you for the honor bestowed on me in elevating me to this honored office as president of your association, and the trust that goes therewith. It is indeed a pleasure to have had the opportunity to serve you in my limited way.

There have been definite advances made in the past year. Some new policies have been adopted and followed, and I believe that they will bear fruit, but progress made in our field is akin to all fields, that it is measured largely by time. I sincerely believe that the institutions of higher learning in our state have become cognizant of health problems existing within the borders of North Dakota more than ever before. The institution of the liaison and health education committees has presented a common front of all these associations, in reviewing and presenting these problems to our educators. The health of a nation is measured by the "grass root" health that exists in that nation. By attacking such problems as a unified group, the liaison committee has accomplished certain things. There have vanished some of the antagonisms that have existed between individual associations through their close contact. The institution of a press-radio-medical conference has opened the door to those people of the press and radio to many of the problems that the medical profession faces, which had never been evaluated except in the light of destructive criticism, heretofore. There was an opportunity presented for constructive criticism which, on the whole, was well received.

As a profession, we still have considerable work to do in improving our public relations. This was well evidenced at the recent legislative session. We as physicians cannot retire into the inner-sanctum of our offices and shield ourselves behind the cloak of medical knowledge and take no active part in community, state, or national affairs. It would behoove us to take a lesson from our barrister cousins, and take positive stands in many of the community problems. I need not remind you that medical education in our state has for all practical purposes been removed from the hands of men who are best qualified and advised on subjects of medical education and placed into the hands of the politician. I need not remind you as to what the national picture was regarding the medical field until the American Medical association took a positive stand and met the issue in the same manner as it was being pushed. We might take a lesson therefrom in our own state and meet organized effort with organized resistance. To do so effectively, we certainly will have to continue in our efforts to improve our public relations. We are truly living in an atomic age, one that is far afield from the "horse and buggy days" practice of medicine fifty years ago. With the advance in knowledge and science and the rapid living, the thinking of those whom we serve has changed through the "dole" system, system of subsidization, and a multitued of other factors that complicate the practice of medicine a thousandfold. Yes, we still have the reverence of many, but they are outnumbered vastly by those who feel that this world is indebted to them along many lines, and one of those lines is health security.

I should like to see the committee on public policy, which is essentially the same as the public relations committee, increase their efforts and activity tremendously. I would like to see this committee appointed to terms on a staggering basis, so that new members may gain knowledge and efficiency as they advance. The finesse of such a committee comes only with experience. It would be my desire to see the council more active in medical problems. This august body is the last appeal of our society in many problems. To me the council should be the driving force within the association.

With your indulgence, may I refer to my message of one year ago relative to the status quo of medicine, the medical profession in our own state of North Dakota. We have agencies in our state, an integral part of our association, set up for the purpose of enlightening the public; the crippled children's program, the education of the exceptional child, the rural hospitalization committee work, within our own organization, and many others where the public may gain information. One of the dilemmas we face at this time is the education of the general public regarding the placement of physicians in rural areas. It is our problem to enlighten the people as to the number of people that are necessary to give the physician a compatible living as well as the number of patients per day in a small hospital for the maintenance and operation of the same on a sound financial basis. It would be my desire to aid such communities by setting up through our executive office a central agency for the classification of localities in need of physicians on a population basis and on the basis of distance to medical centers. Likewise, I would like to see an agency handle the listing of the names of the men who desire a location, thus facilitating matters for the public in their attempt to obtain a medical man for their locality.

Again, may I call to your attention that the physicians' attitude towards one-another is very quickly observed by the laity. It has been often said that the individual with an inferiority complex, less than anyone else, can tolerate or stand a difference of opinion from a fellow worker. Do we, as physicians, all have inferiority complexes? My concept of a difference of opinion is that such is normal and healthy and stimulating to the individual, thus increasing the effort to do better.

As an association, I feel that we should take active steps in the effort to gain attention of our sister association, the North Dakota Nurses association, for the purpose of improving the nursing situation in the hospitals of the state of North Dakota. It is said that by national statistics 2 nurses are required to maintain services to each 3 patients in order to give a satisfactory nursing service. We have approximately 3,000 hospital beds in the state, and if operated at 50 per cent capacity, we have at all times 1,500 patients in our hospitals. This would indicate a minimum need of 500 active nurses in the state of North Dakota to meet set standards. By the same token, we have 9 training schools, 2 to be discredited this year, leaving 7 schools for nurses training

in the state. With a national average of 40 students per school, and many in North Dakota do not begin to meet this number, we are graduating a maximum possible of 280 nurses a year, or a deficit of 220 nurses. This does not take into account the number of girls who are married prior to or immediately after graduation, nor the number who leave the state soon after graduation for fields that are more attractive than nursing in North Dakota. Do we wish more legislation without evaluation of facts, such as happened at the last session, to correct this situation? I do not believe that such would be in the best interest of either the hospitals, nurses, or doctors in this state.

In conclusion, may I call to your attention the 14 points set forth by our executive secretary, Mr. Lyle Limond, in the message of the secretary, published in the handbook. All are worthy of discussion, both pro and con.

May I thank you for your attention, and may some of the points presented here be carried on as I retire into the ranks of the "has-beens."

INAUGURAL ADDRESS

J. SORKNESS, M.D.
Jamestown, North Dakota

It is with a deep sense of humility that I assume this office. Our profession in this state has always occupied a place of high regard in the eyes of our brothers in other states. No small part of this reputation is due to the work of the distinguished men who have preceded me in this office. I feel the honor of this office more deeply because 48 years ago my father occupied the same position; and so far as I know this is the first time that a son of a former president has occupied this office.

Much has been done in the past—a great deal has been done in the past year to further the interest of medicine in our state. Much remains to be done in the future, and I hope that during the coming year we will be able to make a contribution toward this end. I would like to mention a few of the things which we, as a profession, must do to further this work. We must continue to improve our knowledge and ability to practice good medicine. This we must do by stimulating scientific interest and making available to our members scientific programs of genuine help to them. Only by means of an alert, progressive profession will people have available to them the best possible medical care.

We must make this knowledge and ability available to all our people, regardless of race, creed, or economic status. My own feeling is that we have not shirked our duty in this regard. In 28 years of practice, I know of no one who was denied treatment for any reason, if the patient were willing to accept that treatment. We must, however, keep an open mind concerning medical economcis and be willing to explore thoroughly any plan which might possibly improve the distribution of medical care or relieve the burdens of catastrophic illness. I might point out in this connection the fallacy of the term "complete coverage," as related to health insurance. The cost of administering small claims is so disproportionately high that it will never be feasible, in my opinion, to offer such a policy. Our profession has ever been jealous of its right to give freely of its talents without interference by a third party, and insofar as possible, this right should be preserved.

We must make available to the public information which will make them aware of the problems involved in proper medical care. This knowledge should make the public more willing to accept proper medical care and to evaluate medical policy more intelligently, as it applies to all the people.

In the past the people could be depended upon for the right answers, if sufficiently informed, and surely we have no reason to believe that this will change.

Finally, it is our duty to preserve the traditions of our great profession. Our way has been clearly charted by that great procession of physicians who have brought our profession in America to a position unrivaled in the world—all this in less than the time our state society has been in existence.

My efforts during the coming year will be vain without the whole-hearted cooperation and help of all the members of our society. I beg of you this help.

North Dakota State Medical Association Roster-1953

MEMBERSHIP BY DISTRICTS

DEVILS LAKE

Corbett, C. A. ... 316 7th St., Devils Lake
Engesather, J. A. D. ... Box 205, Lakota
Fawcett, D. W. ... Lake Region Clinic, Devils Lake
Fawcett, J. C. ... Lake Region Clinic, Devils Lake
Fawcett, R. M. ... Lake Region Clinic, Devils Lake
Fox, W. R. ... Johnson Clinic, Rugby
Goodman, Edward H. ... Rolla
Gray, Archie G. ... 155 Central Ave. S., Carrington
Johnson, C. G. ... Johnson Clinic, Rugby
Keller, E. T. ... Johnson Clinic, Rugby
Lazareck, I. L. ... 313½ 4th St., Devils Lake
MacDonald, J. A. ... MacDonald Bldg., Cando
Mahoney, J. H. ... 313½ 4th St., Devils Lake
Miles, A. M. ... Rolla
Owens, C. G. ... New Rockford
Palmer, D. W. ... Cando
Pine, L. F. ... Lake Region Clinic, Devils Lake
Pollard, W. S. ... Benson County Clinic, Maddock
Schwinghamer, E. J. ... New Rockford
Seibel, Glenn W. ... New Rockford
Sihler, W. F. (honorary) ... Mann Block, Devils Lake
Stickelberger, Josephine (honorary) ... Oberon
Terlecki, J. ... Minnewaukan
Toomey, G. W. ... Box 703, Devils Lake
Vigeland, G. N. ... Johnson Clinic, Rugby
Voglewede, William C. ... Carrington
White, Frank G. ... Leeds

FIRST

Amidon, Blaine F. ... Dakota Clinic, Fargo
Armstrong, W. B. ... 702 1st Ave. S., Fargo
Bacheller, S. C. ... Enderlin
Bakke, Hans ... Lisbon
Bateman, C. V. ... 310 Dakota Ave., Wahpeton
Beithon, E. J. ... 403 N. 7th St., Wahpeton
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Burt, A. C. ... 405 Black Bldg., Fargo
Christoferson, Lee ... 402 deLendrecie Bldg., Fargo
Clark, I. D. ... Casselton
Corbus, B. C., Jr. ... 304 Black Bldg., Fargo
Darner, C. B. ... 807 Broadway, Fargo
Darrow, F. I. ... 706 8th St. S., Fargo
Darrow, K. E. ... 702 1st Ave. S., Fargo
DeCesare, F. A. ... 702 1st Ave. S., Fargo
Dillard, J. R. ... 314 Black Bldg., Fargo
Dodds, G. A. ... 807 Broadway, Fargo
Donat, T. L. ... 1339 5th Ave. S., Fargo
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Fortin, H. J. ... 313 Black Bldg., Fargo
Fortney, A. C. ... 807 Broadway, Fargo
Foster, George C. ... 15 Broadway, Fargo
Gillam, John S. ... Fargo Clinic, Fargo
Gronvold, F. O. ... 910 Broadway, Fargo
Hall, G. H. ... 807 Broadway, Fargo
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Hawn, H. W. ... Fargo Clinic, Fargo
Heilman, C. O. ... 807 Broadway, Fargo
Hunter, C. M. ... 311 Black Bldg., Fargo
Hunter, G. Wilson ... Fargo Clinic, Fargo
Huntley, H. B. ... Kindred
Irvine, V. S. ... Lidgerwood
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Schneider, J. F. ... 114 Broadway, Fargo
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Craven, J. P. ... 222 Main, Williston
Hagan, E. J. ... 222 Main, Williston
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Johnson, P. O. C. ... Watford City
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McPhail, C. O. ... Crosby
Pile, Duane F. ... Crosby
Skjei, D. E. ... 11½ E. Broadway, Williston
Wright, W. A. ... 11½ E. Broadway, Williston

NORTHWEST

Ayash, John J. ... 119A Main St. S., Minot
Beck, Charles ... Harvey
Blatherwick, Robert ... Parshall
Blatherwick, W. E. ... Newton
Boyum, Lowell E. ... Harvey
Boyum, P. A. ... Harvey
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Cooper, Harry F.	Northwest Clinic, Minot
Craise, O. S.	Towner
Devine, J. L., Jr.	17A Central Ave. W., Minot
Ensign, William G.	Northwest Clinic, Minot
Fischer, V. J.	105 E. Central Ave., Minot
Flath, M. G.	Stanley
Gammell, R. T.	Kenmare
Garland, Thomas F.	Velva
Garrison, M. W.	Garrison Bldg., Minot
Girard, Bernard A.	Mohall Clinic, Mohall
Goodman, Robert	Powers Lake
Greene, E. E.	Westhope
Halliday, D. J.	Kenmare
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Hordinsky, B. Z.	Drake
Huntley, Wellington B.	17 Central Ave. W., Minot
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Johnson, Robert O.	Box 827, Bottineau
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Kermott, L. Henry	12A Main St. S., Minot
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Loeb, George L.	State Hospital, San Haven
Malvey, Kenneth	Bottineau
Naegeli, F. D.	Northwest Clinic, Minot
Nelson, L. F.	104 Simrall, Bottineau
Olson, B. G.	McCannel Clinic, Minot
Pitkin, Olive	Northwest Clinic, Minot
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Seiffert, G. S.	20 4th Ave. S.W., Minot
Shea, Samuel	McCannel Clinic, Minot
Sorenson, A. R.	105 E. Central Ave., Minot
Uthus, O. S.	21½ 2nd Ave. S.E., Minot
Wall, W. W.	20 4th Ave. S.W., Minot
Wallis, Marianne	St. Joseph's Hospital, Minot
Wheelon, F. E. (honorary)	609 9th Ave. S.E., Minot

GRAND FORKS

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Cardy, J. D.	University of North Dakota, Grand Forks
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Goehl, R. O.	221 S. 4th St., Grand Forks
Graham, C. M.	11 N. 5th St., Grand Forks
Graham, John	15½ S. 3rd St., Grand Forks
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Hardy, N. A.	Minto
Haugen, C. O.	Larimore
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Hill, Frank A.	221 S. 4th St., Grand Forks
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Kohlmeyer, A. C.	Larimore
Landry, L. H.	Walhalla
Leigh, Richard	Fargo Clinic, Fargo
Leigh, R. E.	111 N. 5th St., Grand Forks
Liebeler, W. A.	15½ S. 3rd St., Grand Forks
Lommen, C. E.	Fordville
Longmire, Thomas	Sharon
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Muus, J. Meyer	McVille
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Osten, Taylor A.	Michigan
Painter, Robert C.	Grand Forks Clinic, Grand Forks
Panek, A. F.	Milton
Peake, F. Margaret	14½ S. 3rd St., Grand Forks
Piltingsrud, H. R.	Park River
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Rand, C. C.	929 Griggs Ave. S., Grafton
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Ruud, John E.	Box 484, Grand Forks
Ruud, M. B.	Box 484, Grand Forks
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Silverman, Louis B.	221 S. 4th St., Grand Forks
Stratte, J. J.	403 Division Ave., Grand Forks
Strom, Adrian D.	Langdon
Thorgrimsen, G. G.	406 Security Bldg., Grand Forks
Tompkins, C. R.	641 Kittson Ave. S., Grafton
Tompkins, Wm.	641 Kittson Ave. S., Grafton
Turner, R. C.	221 S. 4th St., Grand Forks
Vance, R. W.	4½ S. 3rd St., Grand Forks
Waldren, H. M., Jr.	Drayton
Weed, F. E.	Park River
Witherstine, W. H.	111 N. 5th St., Grand Forks
Woutat, P. H.	221 S. 4th St., Grand Forks
Youngs, N. A.	Grand Forks Clinic, Grand Forks
Lamont, J. G. (honorary)	Grafton

SHEYENNE VALLEY

Christianson, Gunder	Box 789, Valley City
Fennell, William L.	Cooperstown
Gilsdorf, W. H.	125 N.E. 3rd, Valley City
Klein, C. J.	117 N.W. 3rd, Valley City
Macdonald, A. C.	130 Central Ave. S., Valley City
Macdonald, Neil A.	130 Central Ave. S., Valley City
Meredith, C. J.	Box 150, Valley City
Merrett, J. P.	Box 299, Valley City
Van Houten, J.	Valley City
Wakefield, Kenneth	Cooperstown
Wicks, F. L.	726 Chautauqua Blvd., Valley City

SIXTH

Arneson, C. A.	Missouri-Valley Clinic, Bismarck
Bahamonde, Jose M.	Elgin
Baumgartner, C. J.	Quain & Ramstad Clinic, Bismarck
Benson, O. T.	Glen Ullin (North Hollywood, Calif.)
Berg, H. Milton	Quain & Ramstad Clinic, Bismarck
Bertheau, H. J.	Linton
Bodenstab, W. H. (hon.)	520 Mandan St., Bismarck
Boerth, E. H.	Quain & Ramstad Clinic, Bismarck
Boyle, John T.	1 Main St., Garrison
Breslin, R. H.	Mandan
Brink, N. O.	Quain & Ramstad Clinic, Bismarck
Buckingham, T. W.	405 Broadway, Bismarck
Cochran, R. B.	Missouri-Valley Clinic, Bismarck

Dahl, Philip	Missouri-Valley Clinic, Bismarck
Dahlen, G. A.	400½ Main, Bismarck
Davidson, Hugh R.	318 3rd St., Riverdale
DeMoully, O. M.	Flasher
Diven, W. L.	402½ Main Ave., Bismarck
Enders, W. R.	Hazen
Ericksen, Johan A.	409 Washington, Bismarck
Fredricks, L. H.	Quain & Ramstad Clinic, Bismarck
Freise, P. W.	Quain & Ramstad Clinic, Bismarck
Gaebe, O. C.	New Salem
Griebenow, F. F.	905 9th St., Bismarck
Gutowski, Franz	Wishek
Heffron, M. M.	412½ Main Ave., Bismarck
Hetzler, A. E.	104 3rd Ave. N.W., Mandan
Icenogle, Grover	Quain & Ramstad Clinic, Bismarck
Jacobson, M. S.	Elgin
Johnson, Marlin	Quain & Ramstad Clinic, Bismarck
Johnson, Paul L.	Quain & Ramstad Clinic, Bismarck
Kalnins, Arnold	Washburn
Kling, Robert R.	Quain & Ramstad Clinic, Bismarck
Kudinoff, Zoya	Halliday
Kuplis, Haralds	Turtle Lake
LaRose, V. J. (honorary)	522 6th St., Bismarck
Larson, L. W.	Quain & Ramstad Clinic, Bismarck
Levi, W. E.	Beulah
Lipp, G. R.	405 Broadway, Bismarck
McEwen, J. C.	VA Hospital, Livermore, Calif.
Monteith, George	Hazelton
Moses, James	Quain & Ramstad Clinic, Bismarck
Nuessle, R. F.	Quain & Ramstad Clinic, Bismarck
Nugent, M. E.	Quain & Ramstad Clinic, Bismarck
Oja, Karl	Ashley
Owens, P. L.	Missouri Valley Clinic, Bismarck
Perrin, E. D.	Quain & Ramstad Clinic, Bismarck
Peters, Clifford	Quain & Ramstad Clinic, Bismarck
Peterson, Freddie N.	Lac La Belle, Rt. 2, Oconomowoc, Wisconsin
Pierce, W. B.	Quain & Ramstad Clinic, Bismarck
Quain, E. P. (honorary)	2075 Raynor St., Salem, Ore.
Radl, R. B.	Quain & Ramstad Clinic, Bismarck
Roan, M. W.	222 Park St., Bismarck
Salomone, E.	Elgin
Saxvik, R. O.	315 Park St., Bismarck
Schoregge, C. W.	507 6th St., Bismarck
Schoregge, R. D.	507 6th St., Bismarck
Shannon, Dewitt D.	119 2nd St., Riverdale
Spielman, George	107 1st Ave. N.W., Mandan
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
Weyrens, P. J.	Hebron

SOUTHWESTERN

Bush, Clarence A.	Beach
Curiskis, Adolf	New England
Denser, John W.	Bowman
Dukart, C. R.	Dickinson Clinic, Dickinson
Dukart, Ralph	Dickinson Clinic, Dickinson
Gilliland, R. F.	Dickinson Clinic, Dickinson
Gilsdorf, A. R.	Dickinson Clinic, Dickinson
Guloien, H. E.	Dickinson Clinic, Dickinson
Gumper, A. J.	17 Sims St., Dickinson
Gustin, Ralph	Box 71, Beach
Hill, S. W.	Regent
Larsen, Harlan C.	17 Sims St., Dickinson
McNeil, J. H.	Hettinger
Martens, Apollon	Killdeer
Maercklein, O. C.	Mott
Murray, K. M.	Scranton
Reichert, D. J.	24 West Villard St., Dickinson
Reichert, H. L.	24 West Villard St., Dickinson
Rodgers, R. W.	17 Sims St., Dickinson
Schumacher, Wm. A.	Hettinger
Spanjers, Arnold J.	Dickinson Clinic, Dickinson (in Service)
Spear, A. E.	610 1st Ave. W., Dickinson
Tosky, Julian	Richardton

STUTSMAN

Arzt, P. G.	Jamestown Clinic, Jamestown
Beall, John A.	209 2nd St. N.E., Jamestown
Elsworth, J. N.	DePuy-Sorkness Clinic, Jamestown
Fergusson, V. D.	Edgeley
Fisher, A. M.	Box 476, Jamestown
Gerrish, W. A. (honorary)	1801 S. 8th St., Alhambra, Calif.
Gronewald, Tula W.	Box 476, Jamestown
Hayward, Mark	Gackle
Hieb, Edwin O.	DePuy-Sorkness Clinic, Jamestown (in Service)
Hogan, C. W.	205½ 1st Ave. S., Jamestown
Jansonius, J. W.	209 N.E. Third St., Jamestown
Larson, E. J.	DePuy-Sorkness Clinic, Jamestown
Lucy, R. E.	White Bldg., Jamestown
McFadden, R. L.	White Bldg., Jamestown
Martin, Clarence S.	Kensal
Melzer, S. W.	Woodworth
Miles, James V.	722 6th Ave. S.E., Jamestown
Nierling, R. D.	205½ First Ave. S., Jamestown
Oster, Ellis	Ellendale
Pederson, T. D.	Box 951, Jamestown
Sorkness, Joseph	DePuy-Sorkness Clinic, Jamestown
Van Houten, R. W.	Oakes
Woodward, Robert S.	310 10th Ave. N.E., Jamestown (in Service)

TRAILL-STEELE

Buckingham, William M.	Hillsboro
Cleary, Hugh G.	Northwood
Dekker, O. D.	Finley
Kjelland, A. A.	Hatton
Knutson, O. A.	Buxton
LaFleur, H. A.	Mayville
Little, R. C.	Mayville
McLean, Robert William	Hillsboro
Pearson, L. O.	Mayville
Vandergon, Keith G.	Portland
Vinje, Syver	Hillsboro
Waydeman, H. Burrell	Hunter

SEVENTH ANNUAL MEETING
WOMAN'S AUXILIARY TO THE NORTH DAKOTA STATE MEDICAL ASSOCIATION
Minot, North Dakota, May 9, 10, 11, 12, 1953

The seventh annual meeting of the Woman's Auxiliary to the North Dakota State Medical association held in Minot, North Dakota was formally opened by Mrs. G. G. Thorgrimsen, at 10:00 a.m., May 11, 1953, in the Sky Room of the Clarence Parker hotel.

The pledge of loyalty was given by Mrs. Thorgrimsen and repeated in unison by the members present. The group stood together for a silent prayer for peace.

Mrs. J. L. Devine of Minot gave the address of welcome on behalf of the Woman's Auxiliary of the Northwest District. The response was given by Mrs. Stephen Bacheller of Enderlin.

Mrs. Thorgrimsen then introduced Mrs. Henry Kermott, chairman of the convention. She then presented the honored guest and speaker of the convention, Mrs. E. A. Underwood of the national board of directors, Vancouver, Washington.

The roll was called, and the following were present: Mrs. G. G. Thorgrimsen, president; Mrs. L. H. Kermott, Jr., president-elect; Mrs. S. C. Bacheller, first vice-president; Mrs. J. H. Mahoney, second vice-president; Mrs. J. W. Jansonius, recording secretary; and Mrs. I. D. Clark, treasurer.

State chairmen: Mrs. W. A. Lieheler, publicity; Mrs. S. C. Bacheller, program; Mrs. J. H. Mahoney, *Today's Health;* Mrs. R. W. Rodgers, nomination; Mrs. D. J. Halliday, historian; Mrs. L. H. Kermott, organization; Mrs. C. A. Arneson, legislation; Mrs. O. W. Johnson, resolutions.

District presidents: Mrs. G. N. Vigeland, Rugby; Mrs. J. J. Stratte, Grand Forks; Mrs. J. L. Devine, Minot; Mrs. A. K. Johnson, Williston.

Delegates: Mrs. C. J. Baumgartner, Bismarck; Mrs. Lee A. Christoferson, Fargo; Mrs. C. J. Meredith, Valley City; Mrs. A. L. Cameron, Minot; Mrs. A. D. McCannell, Minot; and Mrs. Martin Conroy, Minot.

Councillors: Mrs. Clara Gertson, Grand Forks; and Mrs. O. A. Sedlak, Fargo.

Mrs. Jansonius moved that the minutes of the executive board meeting of the Woman's Auxiliary held in Grand Forks, September 23, 1952 be approved as read. Motion carried.

Mrs. I. D. Clark then read the following treasurer's report:

Financial Report—1952-1953

Receipts:		
Balance on hand, May 1952		$1,776.23
State medical society, convention fund donation	$ 200.00	
Dues	763.00	
Sale of handbooks	4.55	
Sophomore student loan fund	1,191.85	
Total receipts		2,159.40
		$3,935.63
Disbursements:		
Convention expenses	$ 157.00	
Dues to national	254.00	
University of North Dakota sophomore student loan fund	1,225.67	
Purchase of handbooks from national	10.00	
President's expenses:		
National convention	118.51	
Board meeting	74.76	
Discretionary fund	33.60	
Miscellaneous fund	26.75	
President-elect expenses:		
Board meeting	59.50	
Stationery and paper for newsletter	47.89	
Standing committee expenses	14.78	
President's pin	7.99	
Overpayment of dues	10.00	
Bank charges	1.10	
Total dishursements		$2,041.55
Balance on hand, May 1953		1,894.08
		$3,935.63

Motion was made by Mrs. Clark and seconded by Mrs. Berg that the report be accepted. Motion carried.

Mrs. Thorgrimsen then introduced Mr. Lyle A. Limond, executive secretary, North Dakota State Medical association, who brought greetings from the medical association.

Dr. J. Sorkness, incoming president of the state medical association, was then introduced.

A memorial for Mrs. A. W. MacDonald, Valley City, who died during the past year, was read by Mrs. Lieheler of Grand Forks.

The following reports were given by the officers, state chairmen, councillors, and auxiliary presidents:

Organization

The state of North Dakota is fully organized with 10 district auxiliaries to the North Dakota State Medical association. We have a total membership of 245. Of this membership, 208 are active members, 36 associate members, and 1 honorary member.

Number of members according to districts is as follows: Kotana, 10 active; Northwest, 21 active, 3 associate; Southwest, 8 active, 8 associate; Sixth, 36 active, 4 associate; Devils Lake, 12 active, 1 associate; Grand Forks, 39 active, 14 associate; Stutsman, 16 active, 1 associate; Sheyenne Valley, 10 active; Traille-Steele, 7 active, 1 associate; First, 49 active, 4 associate.

Mrs. Mason G. Lawson, Little Rock, Arkansas, is our honorary member.

State committee chairmen are as follows:

Organization and membership—Mrs. S. C. Bacheller, Enderlin.
Program—Mrs. Ted Keller, Rugby.
Today's Health—Mrs. J. H. Mahoney, Devils Lake.
Bulletin—Mrs. Paul Johnson, Bismarck.
Parliamentarian—Mrs. R. W. Rodgers, Dickinson.
Nominating—Mrs. G. G. Thorgrimsen, Grand Forks.
Revisions—(unfilled).
Civil Defense—Mrs. Richard Nierling, Jamestown.
Historian—Mrs. R. J. Halliday, Kenmare.
Legislation—Mrs. C. A. Arneson, Bismarck.
Public Relations—Mrs. John Cartwright, Bismarck.
Nurse Recruitment—Mrs. M. S. Jacobson, Elgin.
Resolutions—Mrs. Joseph Sorkness, Jamestown.
Rural Health—Mrs. G. D. Gertson, Grand Forks.
Sophomore Student Loan Committee:
Mrs. J. D. Cardy, Grand Forks—1954.
Mrs. B. S. Corbus, Jr., Fargo—1955.
Mrs. C. J. Baumgartner, Bismarck (chairman)—1956.
Mrs. Kenneth E. Fritzell, Grand Forks—1957.
Mrs. I. D. Clark, Casselton—1958.

Mrs. L. H. Kermott, Jr., Chairman

Legislation Report

The 1952-53 legislation program was in general favorable to the medical profession in both state and national activities. The 33rd legislative assembly of North Dakota was held this year. Legislation pertaining to the new oil developments in North Dakota outshadowed any medical legislation. Some of the bills which were of interest to the medical association are briefly outlined:

A four-year medical school in operation at the University of North Dakota by 1956 was passed by senate bill No. 184. This bill was probably the one of most interest to the state medical profession, who realized the tremendous expense, the many problems and difficulties of establishing an approved four-year school. It was hoped that the fixed deadline date would not jeopardize the standing of the present accredited two-year medical school at the university.

Aid for the exceptional or handicapped child was contained in senate bill No. 65. This will require the cooperation of the physicians in the examination of children who will receive benefits of the appropriations made in this bill.

The examination and licensure of nurses was covered in senate bill No. 111, which strengthens the professional nurses' examining board.

There were numerous other bills of interest which were passed, some of which are mentioned only briefly: Qualifications of superintendents of the state hospital, the Grafton state school for feebleminded, and the state tuberculosis sanatorium were outlined. Appropriations for the state health department were reduced. Requested appropriations for the state hospital were approved. The state alcoholic commission budget was greatly reduced. The licensing, qualifications, and limitations of practice of chiropodists were outlined in the bill on chiropody.

Nationally, with the newly elected president, who has seemed to be in accord with most recommendations of the American Medical association, the health and legislation program has taken a new role of importance with the establishment of the new department of health, education and welfare in the president's cabinet. The lengthy report of former president Truman's commis-

sion on the health needs of the nation appears to be receiving the careful scrutiny and critical review it deserves with no apparent necessity for any hasty injudicious action.

In spite of the fact that the majority of the American people have demonstrated that they are not in favor of a program of socialism with some form of socialized medicine, this threat on a national basis is ever with us. Recently the danger and seriousness of this threat was emphasized by the activities of tbe international labor organization. The house of delegates of the American Medical association, at their December 1952 session adopted a resolution on "International Treaties and Covenants" to meet this socialistic program of the international labor organization. In brief, this will mean the passage of an amendment to the Constitution of the United States relative to the making of treaties and executive agreements. This has already been proposed as a joint resolution in congress on January 6, 1953 by Senator Bricker along with 63 other senators. The National Medical Auxiliary president stated in her message for the March quarterly bulletin that legislative matters must be given our atention and particularly refers to this resolution. The National Medical Auxiliary chairman on legislation has requested the cooperation of the North Dakota auxiliary in securing at their annual meeting a resolution on international treaties and covenants. In accordance with the recommendations of tbe house of delegates of the American Medical association, the National Medical Auxiliary president, and legislation chairman, the following resolution as recorded by our national legislation chairman in her letter of March 24, 1953 to the state legislation chairman will be presented to the 1953 annual North Dakota State Woman's Medical Auxiliary meeting at Minot for adoption:

RESOLUTION ON INTERNATIONAL TREATIES AND COVENANTS

Whereas, the Woman's Auxiliary to the North Dakota State Medical association has been informed that covenants have been approved by the international labor organization that are in opposition to accepted custom in the United States; and

Whereas, such treaties and covenants are in the first instance adopted by the international labor organization by the vote of representatives who are appointive officials and not elective officials of the United States; and

Whereas, treaties and covenants that have been prepared in such manner are being presented to the congress of the United States for ratification; and

Whereas, the ratification of such treaties would bring results that are contrary to the laws of the United States and the laws of tbe 48 states of the United States; and

Whereas, it is the sense of those attending this state convention that positive action should be taken at this time; now, therefore, be it

Resolved, that the Woman's Auxiliary to the North Dakota State Medical association go on record as disapproving the intent and purpose of such treaties or covenants and that the congress of the United States be memorialized to disapprove and not ratify such treaties and covenants; and be it further

Resolved, that the Woman's Auxiliary to the North Dakota State Medical association reiterate and reaffirm its endorsement of the theory of the proposed amendments to the Constitution of the United States relating to ratification of treaties and covenants which are now pending before the Congress of the United States; and be it further

Resolved, that the Woman's Auxiliary to the North Dakota State Medical association, by resolution, instruct its secretary to send copies of this resolution to all members of the Congress of the United States of America from the state of North Dakota, to the chairman of the Senate Judiciary Committee (Senator William Langer of North Dakota, Senate Office Building, Washington, D.C.), and to the chairman of the House Judiciary Committee (Hon. Chauncey W. Reed of Illinois, House Office Building, Washington, D.C.).

Mrs. Charles A. Arneson, Chairman

Program Report

Each district program chairman is to be congratulated for her part in preparing interesting and constructive programs which were held at the various district meetings during the past year.

An effort has been made to follow suggestions furnished by the national president and such national material as was applicable to our state has been used.

Although our contention is that we are a purely social body, the results of the year's activities would do credit to any type of organization. We can be proud of our record.

The district auxiliaries hold their meetings four times a year. During these meetings there have been three programs on legislation, two on public relations, two on student loan funds, two on community service, two on nurse recruitment, two on civil defense, two on *Today's Health*, and one on physical handicap rehabilitation.

The First district participated in a press conference.

Northwest district helped the patients at Dunseith sell $500 worth of their handicraft.

Several groups raised money for the student loan fund by holding bake sales, teas, selling Christmas decorations, and presenting fashion shows.

In addition to these projects each auxiliary member is assessed $2.00 for the loan fund.

Some districts took part in filter center activities, blood bank programs, and assisting needy families.

All of the organizations took an interest in the past national election.

In addition to all of these activities, social meetings were held with several groups and travel talks were given by their members.

One of the most outstanding activties was the formation of a Medical Students' Wives club. Such an organization was proposed at the 1952 state convention. Under the able guidance of the Grand Forks district, 25 students' wives formed this group.

The Grand Forks district was also outstanding for having printed their year's program in a booklet. This program contains the year's programs, constitution and by-laws, officers, past presidents, representation in the state auxiliary, and names of the chairmen of standing committees.

It would seem appropriate to mention here that North Dakota has had the honor of having Mrs. R. W. Rodgers of Dickinson holding the position of regional chairman for the national program committee for the past year. Her work has entailed supervising and aiding in program planning for the 12 states making up the North Central region. Mrs. Rodgers is the first North Dakota Auxiliary member to be appointed to a national committee in our organization and we can be sure that we are very well represented by her.

Due to the small number of doctors in some counties, it has been necessary to organize the state on a district basis. This immediately presents tbe problem of a scattered membership and reduces the feasibility of 100 per cent cooperation by all members. However, we feel that in spite of our handicap, a very commendable job has been done by each auxiliary and we can look forward to continued success next year.

Mrs. S. C. Bacheller, Chairman

Nurse Recruitment Report

As state recruitment chairman, I felt we should work with other organizations interested in this same program. To this end, I talked with Miss Lewis of the board of nurse examiners in Bismarck, and also to Gladys Wentland, who is the executive secretary of the nursing organization in the state. This resulted in my being appointed on the "student nurse enrollment committee," a group being sponsored by the graduate nurses of the state.

I visited with the registrars at the two schools of nursing in Bismarck. They do have a recruitment program, but neither school has enrolled as many nurses as they are equipped to train. I also corresponded with Mrs. Williams, who is chairman of the committee mentioned above. Just what can be accomplished by all this I do not know, but would like to make the hospitals and nursing organizations throughout the state aware of the fact that we do have a recruitment committee, and that as doctors' wives we are vitally interested in the program, and are willing and anxious to help.

In February, I sent out questionnaires which I received from the district office. Of these, three were returned to me. Two reports showed that little had been done in those districts. Mrs. Cardy of Grand Forks district has been most active. She reports that she canvassed the three schools of nursing and found they have their own recruitment program, but the auxiliary members there provide cars for recruitment teams going to various schools. In addition to this, they contributed $20 to the North Dakota State Nurses association for the student nurse scholarship fund. This money was raised by providing a lunch stand at a "mixer" during the state nurses convention at Grand Forks.

I have at present a film on nursing, "Girls in White," which is supplied by National that we are showing in as many high schools as possible. It has been shown in the Elgin area, and is at present being used here at Minot; from here it will go out to other areas of the state. We are to have it for one month. Our own health department has two good films available to anyone who is interested in them or wishes to use them.

Aside from these things, we also intend to visit schools training practical nurses.

I should like to suggest that when we are no longer raising money for the medical student loan fund, we consider nursing scholarships to be set up in accordance with a training program that is endorsed by the doctors in the state. If I'm not being too presumptuous, I should like also to suggest a cook book compiled and edited by the doctors' wives in the state as a money-raising project.

Mrs. M. S. Jacobson, Chairman

"Today's Health" Report

Although we did not reach our quota of 232 for *Today's Health* subscriptions, each district has sold a few, and in Devils Lake and Southwestern, over 200 per cent of their quota was sold,

making them members of "Today's Health More Exclusive Club," which is quite an honor. Following is the listing by districts, their quotas, the number of subscription credits secured, and the percentages for each, as well as the totals for the state:

District	*Quota*	*Credits*	*Percentage*
Devils Lake	13	32	246
First	49	5	10
Grand Forks	52	23	44
Kotana	9	5	56
Northwest	24	6	25
Sheyenne Valley	10	6	60
Sixth	38	22	58
Southwestern	15	32	213
Stutsman	18	7½	42
Traill-Steele	8	0	0
State Totals	232	138½	60

Mrs. J. H. Mahoney, Chairman

Bulletin Report

Bulletin subscriptions have increased from 12 subscriptions to 55.

Mrs. P. B. Johnson, Chairman

Historian's Report

Mrs. D. J. Halliday compiled many interesting articles in a "Scrapbook." This scrapbook was on display at our convention.

Mrs. D. J. Halliday, Chairman

Public Relations Report

The most outstanding public relations meeting was our meeting with the press.

All auxiliaries cooperate with civic organizations.

All contribute to the A.M.A. Education foundation.

In my opinion, the filter center in Fargo is the most outstanding participant in civil defense activities.

All auxiliaries cooperate in some way or other with state or local health departments on their projects.

All auxiliaries actively cooperate with health and welfare agencies. Their outstanding activity is the crippled children's program.

One of the miscellaneous public relations projects is the donation to the Underprivileged Boy's Home, Mapleton, North Dakota.

Mrs. J. C. Swanson, Chairman

President's Report

The Woman's Auxiliary to the North Dakota State Medical association extends greetings to our national president, Mrs. Ralph Eusden, and to the officers and members of the Woman's Auxiliary to the American Medical association.

The presidency of the auxiliary has been a most enjoyable experience. It has been especially pleasant because of the marvelous cooperation from the members of the board, the standing committees, and all of the members of the Woman's Auxiliary.

An amazing amount of energy is shown in the reports of the district presidents. The social side has played an important role in the development of the Woman's Auxiliary not only from the entertainment angle, but in cultivating friendly relations and promoting mutual understandings on the county and state levels.

North Dakota has 10 districts with a total membership of 240. As there are only 340 doctors in the state, this percentage is good.

The annual state board meeting was held in Grand Forks on September 23, 1952. Plans were outlined for the year's activities. Dr. P. H. Wontat, Grand Forks, was guest speaker.

Copies of *Today's Health* have been placed in public schools, school libraries, and doctors' and dentists' offices.

Bulletin subscriptions have greatly increased. The accomplishments of the auxiliaries from counties, states, and national is published as well as many editorials. Being an informed member and knowing the works of its auxiliary is vitally important. It is an acknowledgment of the achievements of its members.

As doctors' wives, auxiliary members are vitally interested in the health and welfare of their community. Its members have worked closely with all health agencies such as the American Cancer society, the Heart association, Tuberculosis association, the National Polio Foundation, and the National Foundation for Infantile Paralysis.

They have participated in many community services including the various branches of Red Cross activities, blood banks, mental health programs, crippled children's programs, and many others. The hospitals in the state have benefited greatly by the works of the auxiliary. The members have donated equipment and given services in innumerable ways. They have also assisted in organizing active hospital auxiliaries.

Assistance has been given the nurse recruitment program. Medical auxiliary members were hostesses to the state nurses association at their mixer during their state convention.

Mrs. R. H. Rodgers, Dickinson, was regional chairman for the national program committee for the past year.

North Dakota is primarily a rural state. A suggestion was made that the chairman of the council on rural health be assisted by the Woman's Auxiliary to the North Dakota State Medical association. The rural health committee met with the combined state rural health and state public health at a conference, October 10 and 11, 1952. Dr. W. A. Wright, Williston, was moderator at a panel discussion on the following topics: "Problems in hiring and training nurses for the rural hospitals"; "Administration problems in rural health"; "Cleanliness and sanitation"; "Public health problems in rural areas." Dr. O. W. Johnson, Rugby, president of the state medical society, and Mr. Aubrey D. Gates, field director, participated in the panel discussion.

Our civil defense committee has offered its assistance to local district defense committee, if and when it becomes necessary.

The thirty-third legislative assembly of North Dakota was held this year. Legislation pertaining to the new oil developments in North Dakota far outnumbered any medical legislative bills.

A four-year medical school in operation at the University of North Dakota by 1956 was passed by senate bill 184. This bill was probably the one of most interest to the state medical profession. It was hoped that the fixed deadline would not jeopardize the standing of the present accredited two-year medical school at the university.

Aid for the exceptional or handicapped child was contained in senate bill 65. This will require the cooperation of the physicians in the examination of children who will receive benefits of the appropriation made in the bill.

The examination and licensure of nurses was covered in senate bill 111, which strengthens the professional nurses' examining board. Qualifications of superintendent of the state hospital, state school for feebleminded, and the state tuberculosis sanatorium were outlined. Appropriations for the state hospital were approved. The state alcoholic commission budget was greatly reduced. The licensing, qualifications and limitations of practice of chiropodists were outlined in the bill on chiropody.

The following addresses were given: "The president's commission on the health needs of the nation"; "Needs and rehabilitation of the handicapped child"; "Importance of the hospital laboratory to the community"; "Training of technicians"; "Blood banks." Short addresses were given by some of the members of the league of women voters. The speaker from the National Foundation for Infantile Paralysis was Mrs. Doris Smith, Enderlin, North Dakota.

A 15-minute radio program entitled "Woman Talk" has been conducted by one district auxiliary member who uses a fictitious name.

One district auxiliary had the distinction of having a member who is the sister of Mrs. E. A. Allen, former national president, Atlanta, Georgia, who visited the district this year.

One district was saddened by the death of the wife of a long time physician and surgeon.

Many of the auxiliary members took an active interest in the church work of their community.

A Christmas benefit tea was held in December by one district. Food, clothing, and money to amply supply two needy families at Christmas time was given by one auxiliary. Merchandise made by the patients at San Haven tuberculosis sanatorium was sold by auxiliary members and returned to patients for their needs.

Money was contributed to the Good Samaritan boys' camp.

These activities were interspersed with social and cultural programs. Lectures on music, book reports, and interesting travel talks were given by some auxiliaries.

Twenty-eight women who are wives of University of North Dakota medical students were organized under the direction of the auxiliary and given the name "Medical Students' Wives club."

Of interest to all district auxiliaries is the statewide sophomore medical student loan fund project. It is the tie that binds us together. Through the activity of raising money, we have learned to know one another better.

Our activities include formal teas, style shows, lottery tickets, bake sales, card parties, personal donations, and rummage sales.

The News Letter keeps us informed about the personal activities of the auxiliary members.

As president of the woman's auxiliary, I attended the national convention in Chicago, June 8-13, 1952. My contact there with the national officers was an inspiration.

It was gratifying to note the recognition the woman's auxiliary is now receiving. Mrs. Henry Kermott, Jr., president-elect, and I attended the national conference in Chicago, November 6 and 7, 1952.

Our annual state convention will be held in Minot, May 10-12, 1953. We will have as our honored guest and speaker, Mrs. E. A. Underwood of the national board of directors, Vancouver, Washington.

I was the guest of honor at the Minnesota medical auxiliary's state meeting in St. Paul May 18-20.

Our thanks to the central office in Chicago and the North Dakota state medical society office is extended with gratitude for the many favors they have given in assisting in our work.

Mrs. G. G. Thorgrimsen, President

Auxiliary President's Report—First District

The auxiliary to the First District medical society held four meetings during the current year. At our first meeting we joined the doctors at the press relations conference. Our programs for the following meetings included a book report, travel talk, and a talk on modern music.

We sent our yearly contribution of $25 to Good Samaritan boys' camp.

The annual bake sale was held April 25 to raise money for the student loan fund. Our contribution was $236.

Officers for the year have been: president, Mrs. R. D. Weible; vice-president, Mrs. John LeMar; secretary, Mrs. Robert Rogers; treasurer, Mrs. Lee Christoferson.

Mrs. R. D. Weible, President

Auxiliary President's Report—Second District

At the beginning of the season, it was unanimously agreed upon that, with the exception of a donation to the medical student loan fund, our meetings would be social. Donations to this fund are being raised through the sale of tickets.

We have sixteen members, with the following officers: president, Mrs. C. A. Corbett, Devils Lake; secretary, Mrs. I. L. Lazarek, Devils Lake; councillor, Mrs. E. T. Keller, Rugby.

Mrs. C. A. Corbett, President

Auxiliary President's Report—Third District

This group has 53 members in good standing, of which 4 are associate members.

Four meetings were held during the year. One, honoring Mrs. G. G. Thorgrimsen, president of our state organization, was held in the afternoon; three were regular dinner meetings.

Dr. O. W. Johnson, president of the North Dakota State Medical association, and Mr. Limond, secretary of the same organization, honored us with their presence at one of our meetings.

Mrs. Robert Griffith, president of the league of women voters, was guest speaker at our meeting prior to the national election. Her topic was "Get Out and Vote."

Programs of music and the showing of kodachrome slides on Paris and London were arranged for the other meetings.

Our activities in the nurse recruitment program are limited; for in the three schools of nursing here, each has a definite recruitment program of its own. However, many of our members are called on to drive these recruiting teams to the surrounding high schools.

During the fortieth convention of the North Dakota State Nurses association, this auxiliary participated in their program. A contribution of $20 was made to the state student nurses' scholarship fund.

As suggested at the convention in Fargo in 1952, the wives of the medical students at the University of North Dakota have organized as the "Medical Students' Wives' club." Mrs. G. G. Thorgrimsen, state president; Mrs. J. D. Cardy, member of our group and of the faculty wives' club, and I, have acted in an advisory capacity. These young women show a great deal of enthusiasm and interest and meet regularly once a month.

Many of our members have held high office and taken a very active part in the following organizations: Red Cross, American cancer society, St. Michael's hospital auxiliary, crippled children's program, P.T.A., Grand Forks symphony association, local church groups and so forth.

A style show featuring children's clothes was our first activity towards money raising for the sophomore medical student loan fund. Other activities planned were cancelled due to the Quota club's sponsoring a rummage sale for funds for the YWCA. We contributed our rummage to their effort. Then, in order to increase our contribution to the student loan fund, voluntary donations were made by the members. The total for the year was $158.85.

Fifteen renewals and eight new subscriptions to *Today's Health* were obtained; six new and six renewals for *The Bulletin*.

The following officers were elected for the year 1953-1954: president, Mrs. R. O. Goehl; vice-president, Mrs. H. D. Benwell; secretary, Mrs. W. C. Dailey; treasurer, Mrs. E. L. Grinnell; and for a three-year term, councillor, Mrs. G. D. Gertson.

Mrs. R. O. Goehl was installed in office at our April meeting.

Mrs. J. J. Stratte, President

Auxiliary President's Report—Fourth District

The following notes cover most of the activities of the auxiliary to the Northwest District Medical association. With the exception of the summer recess and the months of November and December, the auxiliary met once a month. The business meetings were preceded by dinner and usually followed by a program. All meetings were held in Minot.

September: Organization meeting. Committee appointed. The following officers took over their duties: president, Mrs. J. R. Pence; vice-president, Mrs. R. T. Gammell; secretary, Mrs. V. J. Fischer; terasurer, Mrs. M. T. Lampert.

October: Business meeting followed by a program. Miss Rhodes, physical therapist from St. Joseph's hospital, Minot, talked to the group on "Needs and rehabilitation of the handicapped child."

January: Business meeting followed by a program. Margaret Aune of the Union Travel agency gave a talk on her latest European tour and showed colored slides.

February: Business meeting followed by a program. Miss Hester Johnson, chief technologist from Trinity hospital, Minot, read a paper. The subject matter included "Importance of the hospital laboratory to the community," "Training of technicians," and "The blood bank."

March: This meeting was postponed until early April when a business meeting was held.

April: Business meeting with election of officers. Mrs. Henry Kermott, general chairman of the convention committee, outlined the plans for the state convention. The program consisted of motion pictures from the Cancer society. The following officers were elected: president, Mrs. J. L. Devine, Jr.; vice-president, Mrs. P. J. Breslich; secretary, Mrs. Roger Sorenson; treasurer, Mrs. M. T. Lampert.

Activities:

San Haven project: Merchandise made by the patients at San Haven tuberculosis sanatorium was sold in Minot. Mrs. A. R. Sorenson, chairman, reported that the two sales brought in approximately $500.

Hospital Guilds: Auxiliary members assisted the guilds of both St. Joseph's and Trinity hospitals in Minot.

Student Loan: The auxiliary raised $75 for the student loan fund.

Mrs. Robert Gammell, Vice-President

Auxiliary President's Report—Fifth District

The Woman's Auxiliary to the Sheyenne Valley medical society has a membership of 10. One new member was added and 1 lost the past year.

The organization has 5 subscriptions to *Today's Health* and 1 to *The Bulletin*.

Meetings are mainly social with the student loan fund, community service, and assistance to the local hospital the main projects.

Officers for the coming year are: president, Mrs. Paul Merrett; secretary-treasurer, Mrs. Fred Wicks.

Mrs. G. Christianson, President

Auxiliary President's Report—Sixth District

The Woman's Auxiliary to the Sixth district medical society has 40 active paid-up members. There has been an appreciable gain in memberships over last year.

There are four auxiliary meetings a year. These are usually dinner meetings with a program and we have averaged 25 members at these meetings. Our first meeting of the fiscal year was held on October 21, 1952. An interesting address was given on "The President's commission on the health needs of the nation." The second meeting was held December 2, 1952. Mrs. C. W. Schoregge gave an educational travel talk and pictures on her recent trip in Europe. The third meeting was held February 24, 1953. The topic was the proposed bills on legislation by Mrs. C. A. Arneson, our state legislation chairman. An active discussion followed the presentation of the bills. The rest of the evening was spent informally honoring our departing auxiliary member, Mrs. E. Salamone, Elgin.

One of the highlights of our activities for the year was the tea and style show at the Apple Creek Country club, headed by Mrs. R. Waldschmidt. The proceeds will go to the student loan fund.

It is planned to have a fourth meeting the last of April or the first part of May. At this meeting, there will be election of officers and the naming of delegates to the state auxiliary medical convention.

Mrs. John T. Cartwright, President

Auxiliary President's Report—Seventh District

The Stutsman County Women's Medical auxiliary opened the 1952-53 year with a dinner meeting on October 28, 1952. We were honored at this meeting by a visit from our state president, Mrs. G. G. Thorgrimsen, and by Mrs. E. A. Allen of Atlanta, Georgia, former national president to the women's medical auxiliary. Both guests gave some very excellent talks. Mrs. Allen with her vast experience was a rare treat to such a small group.

A Christmas tea was held in December, at which time members contributed canned goods, clothing, and money to amply supply two needy families. Dr. R. S. Woodward, as guest speaker, discussed health problems.

Our project this year was the student loan fund, and it was taken care of by cash contributions from each individual member. A check for $75 has been mailed to Mrs. I. D. Clark, our state treasurer.

In February, we had another dinner meeting with the following

guests: Sister Carita, superintendent of nurses at Trinity hospital; Sister St. Mary and Miss Mathilde Haga, directors of nursing education, Jamestown college; and Mrs. Gilbert Horton. Sister Carita and Miss Haga gave talks on nursing. Mrs. Horton told us about our camp Rockiwan for boys and girls at Spiritwood Lake. Mrs. John W. Jansonius, secretary to the state auxiliary, gave a review of the state meeting in Fargo.

A fourth meeting in April will conclude the active year.

Six subscriptions to *Today's Health* were obtained.

The Stutsman County auxiliary totals 17 members, including wives from Jamestown, LaMoure, and Edgeley.

I am happy to mention that practically all our members have taken a very active part in contributing to the efforts of the cancer drive, polio, and Red Cross.

MRS. GEORGE H. HOLT, President

Auxiliary President's Report—Eighth District

We have 10 members, 9 of them from Williston and 1 from Crosby.

This past year we had a dinner meeting on the same evening as the county medical society meeting and found this to be much more successful.

We gave 5 subscriptions of *Today's Health*—one to each of the following: Williston high school, Good Samaritan and Mercy hospitals in Williston, Crosby hospital, and to the Watford City hospital. We also gave $50 to the student loan fund.

MRS. A. K. JOHNSON, Alternate Delegate

Auxiliary President's Report—Traill-Steele District

As you probably know, our district meetings are primarily social in origin as weather and distances rarely permit anything else. This winter has been an exception, of course. Our membership totals 8; we lost 1 former member, but gained 4 new ones. We meet 4 times a year. We have dinner meetings with our husbands; then each group has a separate business meeting, but a joint social period. We make cash contributions to the student loan project.

We should like to send greetings to the members of the auxiliary, and will be anxious to hear about the convention in Minot.

MRS. K. G. VANDERGON, President

Auxiliary President's Report—Tenth District

The Women's Auxiliary to the Southwestern District medical society respectfully submits the following report for 1952 and 1953:

Auxiliary members assisted the Sisters of St. Joseph's hospital with the reception and open house they held in connection with the opening of the new hospital wing. The ladies took groups through the building and helped with the refreshments. The group also presented the hospital with a check to be used to furnish the linens for a room in the new wing.

Auxiliary members contributed to the student loan fund as they have each year since this fund was established.

The Southwestern district was informed by the national chairman of *Today's Health* that we were one of the highest groups in the nation in point of subscriptions for last year. Thus encouraged, we made that one of our main objectives of the year. To date we have sold 33 subscriptions.

Auxiliary members assisted the state health department in giving audiometer tests when they checked the hearing of all the students in the local schools this winter.

The auxiliary has plans for a rummage sale for which Mrs. R. W. Rodgers is chairman. The members are working on this project at present and the sale is scheduled to be held sometime in May.

MRS. H. L. REICHERT, President

Press and Publicity Report

I believe that there should be a deadline date for receiving the news to be edited. We have published only three newsletters this year instead of four, since the news has been held up somewhere along the line.

MRS. W. A. LIEBELER, Chairman

Nominations Report

President—Mrs. Henry Kermott, Jr., Minot
President-elect—Mrs. S. C. Bacheller, Enderlin
First Vice-president—Mrs. J. H. Mahoney, Devils Lake
Second Vice-president—Mrs. C. A. Arneson, Bismarck
Recording secretary—Mrs. J. W. Jansonius, Jamestown
Treasurer—Mrs. V. J. Fischer, Minot

MRS. R. W. RODGERS, Chairman
MRS. A. E. SPEAR
MRS. A. J. GUMPER

Motion was made by Mrs. Rodgers, seconded by Mrs. Christoferson, that we adopt the reports. Motion carried.

Meeting adjourned to reconvene at 2:00 p.m., Sky room, Clarence Parker hotel.

A very interesting luncheon was held Monday, May 11, in the Silver Saddle room, Clarence Parker hotel. Mrs. Paul E. Smith, Enderlin, gave us some very helpful facts about infantile paralysis.

The convention reconvened at 2 o'clock p.m., May 11, 1953. The meeting was called to order by Mrs. G. G. Thorgrimsen, president.

Mrs. 1. D. Clark read the following proposed budget for 1953-1954:

Income

Dues, 250 members at $2.00	$500.00

Proposed Expenditures

President:	
1. Discretionary fund (visiting districts, entertaining guests, etc.)	$ 35.00
2. Miscellaneous fund (telegram, telephone, and postage)	15.00
3. Board meeting (railroad fare, hotel room, and board meeting expenses)	100.00
4. National convention (railroad fare, hotel room, and convention expenses)	200.00
President-elect:	
1. Board meeting (railroad fare, hotel room, and board meeting expenses)	100.00
Standing committees (postage, telephone, telegram, and expenses)	25.00
Miscellaneous	25.00
	$500.00

Motion was made by Mrs. Rodgers, seconded by Mrs. Berg, that we adopt the proposed budget. Motion carried.

Mrs. Clark also read a letter of appreciation, for paying her national dues, from Mrs. Mason G. Lawson, national treasurer and honorary member of our North Dakota woman's auxiliary. It was moved by Mrs. Rodgers, seconded by Mrs. Devine, that we again pay her dues for 1953-1954.

Mrs. R. W. Rodgers, chairman of the nominating committee, then submitted the following report:

Nominating Committee Report

President—Mrs. Henry Kermott, Jr., Minot
President-elect—Mrs. S. C. Bacheller, Enderlin
First vice-president—Mrs. J. H. Mahoney, Devils Lake
Second vice-president—Mrs. C. A. Arneson, Bismarck
Recording secretary—Mrs. J. W. Jansonius, Jamestown
Treasurer—Mrs. V. J. Fischer, Minot

Mrs. Thorgrimsen then asked for nominations from the floor for these offices. As there were none, she asked for a motion nominating the slate of officers. It was moved by Mrs. Rodgers, seconded hy Mrs. Berg, that we instruct the secretary to cast a unanimous hallot for the entire slate of officers. All voted "aye".

The secretary was then instructed to send a letter of appreciation for the many courtesies throughout the year to Mrs. Freming and Mr. Limond.

Mrs. R. W. Rodgers and Mrs. G. D. Gertson were appointed to audit the books.

Motion was made hy Mrs. Berg, seconded by Mrs. Liebeler, that we buy a gavel for the auxiliary. Motion carried.

Mrs. Licheler hrought up the question of a registration fee at our convention to help defray the cost. Motion was made by Mrs. Bacheller, seconded hy Mrs. Berg, that we have a registration fee of $1.00 at our convention. Motion carried.

Mrs. P. E. Johnson, Bismarck, and Mrs. S. C. Bacheller, Enderlin, were chosen as our delegates to the national convention to be held in New York City, June 1.

The secretary read the following report of the sopbomore medical student loan fund covering the period from July 1, 1951 to May 1, 1953:

Year, Month, Day	*Debits*	*Credits*	*Balance*
1951—July 2		$1,047.76	$1,047.76
July 30	$500.00		547.76
December 7	500.00		47.76
1952—August 25		1,225.67	1,273.43
Decemher 26	400.00		873.43
1953—January 12	400.00		473.43
February 10	400.00		73.43

E. W. OLSON, Business Manager,
University of North Dakota

Sophomore Student Loan Fund Project Receipts
1952-1953

Devils Lake district	$ 80.00
First district	236.00
Grand Forks district	158.85
Kotana district	50.00
Northwest district	75.00
Sheyenne district	15.00
Sixth district	400.00
Southwestern district	32.00
Stutsman county district	75.00
Total	$1,121.85

Resolutions Report

I.

Whereas, the president, Mrs. G. G. Thorgrimsen, has served the Woman's Auxiliary to the North Dakota State Medical association faithfully and well; and

Whereas, under her leadership a prosperous and successful year has been enjoyed, and

Whereas, her efforts have led to wider recognition of the Woman's Auxiliary to the North Dakota State Medical association, therefore he it

Resolved, that the Woman's Auxiliary to the North Dakota State Medical association, in convention assemhled in Minot, May 11, 1953, extend to Mrs. G. G. Thorgrimsen its heartfelt thanks and sincere appreciation for the great service that she has rendered to that group.

II.

Whereas, the Woman's Auxiliary to the North Dakota State Medical association has held its seventh annual meeting in Minot, and

Whereas, the Woman's Auxiliary to the Northwest District medical society has served as hostess during the meeting and has performed its function so admirahly, and

Whereas, the North Dakota State Medical association and the Northwest District medical society have assisted in this convention, and

Whereas, the manager of the Clarence Parker hotel and staff have provided excellent accommodations and service, and

Whereas, the Minot Country cluh for the use of their beautiful facilities, and

Whereas, the woman's group of the All Saints Episcopal church for their gracious extension of hospitality, and

Whereas, the Minot *Daily News* for their courtesies and puhlicity, and

Whereas, Mr. Lyle A. Limond, executive secretary for the North Dakota State Medical association, for his continued efforts in our hehalf and his promise of future assistance, and

Whereas, Dr. J. Sorkness of Jamestown, persident-elect, for his presence and inspiration, and

Whereas, to Mrs. E. A. Underwood of the national board of directors, Vancouver, Washington, for her presence and gracious assistance rendered this seventh annual meeting, and

Whereás, to Mrs. D. J. Halliday for preparing the very interesting scrapbook for the seven-year historical events of the auxiliary, and

Whereas, Mrs. Doris Smith of Enderlin, head of the women's activities committee of the National Foundation for Infantile Paralysis, through her efforts at this meeting and other meetings throughout the state of North Dakota in the organization of a woman's corps for the purpose of aiding and assisting in the care of polio cases in our hospitals is rendering a service to this auxiliary and to the population at large in the state of North Dakota, he it

Resolved, that the Woman's Auxiliary of the North Dakota State Medical association extend a vote of thanks to Mrs. Doris Smith.

Mrs. O. W. Johnson, Chairman

A delightful banquet was held Monday, May 11, 6:00 p.m., at the All Saints Episcopal church. Mrs. E. A. Underwood of the national board of directors, Vancouver, Washington, was our honored guest and speaker. She stressed the promotion and sales of *Today's Health* magazine—the main puhlication hy which health material reaches the public.

A very interesting fact in her address was that the woman's auxiliary was organized directly from the house of delegates in 1922, and that it took 28 years to organize an auxiliary in every state. It was not until 1945 that we were requested to alert the puhlic and memhers on some of the far-reaching factors of medical legislation.

Mrs. Underwood gave some very interesting statistics about the prepaid medical plan; how in 1949 a request was made for an NEA campaign in each auxiliary. She praised the medical student loans since it was one step toward freeing us from constantly seeking a "federal Santa Claus."

She stressed the tremendous power of the vote, and the urgent need for being well informed on medical legislation.

Our last husiness session and social program was a brunch at the Minot Country cluh, Tuesday, May 12, 10:30 a.m.

After the hrunch, Mrs. E. A. Underwood congratulated the incoming officers on their new duties, and installed them in their offices. She presented each with a rose corsage from Portland, Oregon.

Mrs Thorgrimsen turned over the files to Mrs. Henry Kermott.

The meeting was then adjourned.

Postconvention Minutes

Mrs. Kermott called the meeting to order. She presented and thanked her associates for their assistance in convention planning and work. She thanked the auxiliary for selecting her as its president.

1953 MEMBERSHIP ROSTER
WOMAN'S AUXILIARY TO THE NORTH DAKOTA STATE MEDICAL ASSOCIATION

MEMBERSHIP BY DISTRICTS

First

Amidon, Mrs. B. B. ..... 1705 5th Ave. S., Fargo
Armstrong, Mrs. William B. ..... 1248 9th St. N., Fargo
Bacheller, Mrs. Stephen C. ..... Enderlin
Baillie, Mrs. W. F. ..... 719 Broadway, Fargo
Bateman, Mrs. Clarence V. ..... 529 4th St. N., Wahpeton
Beithon, Mrs. E. J. ..... 429 N. 5th St., Wahpeton
Bond, Mrs. John H. ..... 516 13th St. S., Fargo
Borland, Mrs. Verl G. ..... 1514 9th St. S., Fargo
Burton, Mrs. John P. ..... 804 8th St. S., Fargo
Burton, Mrs. P. H. ..... 415 8th St. S., Fargo
Clark, Mrs. Ida D. ..... Casselton
Corhus, Mrs. Budd C., Jr. ..... 1251 4th St. N., Fargo
Darrow, Mrs. Kent ..... 716 S. 8th St., Fargo
DeCesare, Mrs. Francis A. ..... 1401 9th St. S., Fargo
Dillard, Mrs. J. R. ..... 620 S. 8th St., Fargo
Elofson, Mrs. Carl E. ..... 1334 3rd St. N., Fargo
Fortin, Mrs. H. J. ..... 1440 S. 8th St., Fargo
Fortney, Mrs. A. C. ..... 1122 S. 9th St., Fargo
Gillam, Mrs. John S. ..... 1503 6th St. S., Fargo
Hall, Mrs. George H. ..... 1250 5th St. N., Fargo
Hanna, Mrs. James F. ..... 907 12th Ave. S., Fargo
Haugrud, Mrs. Earl M. ..... 1310 N. 3rd St., Fargo
Hawn, Mrs. Hugh W. ..... 1325 1st St. N., Fargo
Heilman, Mrs. Charles O. ..... 1338 2nd St. N., Fargo
Hunter, Mrs. Cornelius M. ..... 1434 6th St. S., Fargo
Irvine, Mrs. Vincent S. ..... Lidgerwood
James, Mrs. J. B. ..... St. John's Hospital, Fargo
Lancaster, Mrs. William E. G. ..... 1437 8th St. S., Fargo
Larson, Mrs. G. Arthur ..... 1538 9th St. S., Fargo
LeBien, Mrs. Wayne E. ..... 1353 5th St. N., Fargo
LeMar, Mrs. John D. ..... 1249 10th St. N., Fargo
Lewis, Mrs. Thomas H. ..... 121 5th St. N., Fargo
Long, Mrs. William H. ..... 1438 8th St. S., Fargo
Lytle, Mrs. Francis T. ..... 1301 Broadway, Fargo
Melton, Mrs. Frank M. ..... 1545 6th St. S., Fargo
Mazur, Mrs. Bernard A. ..... 1237 3rd St. N., Fargo
Moe, Mrs. Allen E. ..... 1112 6th Ave. S., Moorhead, Minn.
Poindexter, Mrs. Marlin H. ..... 1350 9th St. S., Fargo
Pray, Mrs. Laurence G. ..... 1526 7th St. S., Fargo
Rogers, Mrs. Robert G. ..... 1217 7th St. S., Fargo
Sedlak, Mrs. Oliver A. ..... 1019 9th St. S., Fargo
Schneider, Mrs. Joseph F. ..... 901 13th St. S., Moorhead, Minn.
Stafne, Mrs. William A. ..... 1409 9th St. S., Fargo
Swanson, Mrs. Joel C. ..... 1220 8th St. S., Fargo
Thompson, Mrs. Andrew M. ..... 313 7th St. N., Wahpeton
Urenn, Mrs. Bernard M. ..... 1005 9th St. S., Fargo
Weihle, Mrs. R. E. ..... 714 8th St. S., Fargo
Weible, Mrs. Ralph D. ..... 1628 9th St. S., Fargo
Wold, Mrs. Lester E. ..... 912 13th St. S., Moorhead, Minn.

Devils Lake

Fawcett, Mrs. Donald W. ..... 1105 5th St., Devils Lake
Fawcett, Mrs. John C. ..... 1125 5th St., Devils Lake
Fawcett, Mrs. Robert M. ..... 816 9th St., Devils Lake
Fox, Mrs. William R. ..... 315 2nd Ave. E., Rugby
Goodman, Mrs. Edward A. ..... Rolla
Johnson, Mrs. Christian G. ..... 309 3rd St. W., Rughy
Keller, Mrs. E. Theodore ..... 317 3rd St. E., Rughy
Mahoney, Mrs. James H. ..... 803 6th St., Devils Lake
Pine, Mrs. L. F. ..... 919 3rd St., Devils Lake
Pollard, Mrs. William S. ..... Maddock
Terlecki, Mrs. Jaroslaw ..... Minnewaukan
Toomey, Mrs. Glenn W. ..... 418 7th St., Devils Lake
Vigeland, Mrs. George N. ..... Rugby

Grand Forks

Alger, Mrs. Leon J. ..... 81 4th Ave. S., Grand Forks
Arneson, Mrs. A. O. ..... 419½ 5th St. S., Grand Forks
Benson, Mrs. Theodore Q. ..... 1101 Reeves Drive, Grand Forks
Benwell, Mrs. Harry D. ..... 625 3rd St. S., Grand Forks
Cardy, Mrs. James D. ..... 1515 Oak St., Grand Forks
Culmer, Mrs. A. E., Jr. ..... 1503 Oak St., Grand Forks

Dailey, Mrs. Walter C.	1118 Reeves Drive, Grand Forks
Folsom, Mrs. John D.	612 Lincoln Court, Grand Forks
Fritzell, Mrs. Kenneth E.	1125 Reeves Drive, Grand Forks
Gertson, Mrs. G. D.	511 5th St. S., Grand Forks
Goehl, Mrs. R. O.	1015 Reeves Drive, Grand Forks
Graham, Mrs. Charles N.	923 Almonte St., Grand Forks
Graham, Mrs. John H.	502 Lincoln Court, Grand Forks
Grinnell, Mrs. Ernest L.	1207 Lincoln Drive, Grand Forks
Haunz, Mrs. Edwin A.	1029 Lincoln Drive, Grand Forks
Hill, Mrs. Frank A.	1521 Oak St., Grand Forks
Hofto, Mrs. J. M.	321 4th St. N., Grand Forks
Jensen, Mrs. August F.	1721 Belmont Rd., Grand Forks
Johann, Mrs. O. P.	Grafton
Kohlmeyer, Mrs. A. C.	Larimore
Landry, Mrs. L. H.	Walhalla
Leigh, Mrs. Richard E.	17 Conkling Ave., Grand Forks
Liebeler, Mrs. W. A.	So. Washington, Grand Forks
Lommen, Mrs. C. E.	Fordville
Mahowald, Mrs. Ralph E.	606 5th St. S., Grand Forks
Moore, Mrs. John H.	1114 Reeves Dr., Grand Forks
Mulligan, Mrs. Thomas	514 Belmont Rd., Grand Forks
Muus, Mrs. O. Harold	59 4th Ave. S., Grand Forks
Painter, Mrs. Robert C.	1121 Belmont Rd., Grand Forks
Porter, Mrs. Charles B.	1210 Chestnut St., Grand Forks
Potter, Mrs. Paul	2024 2nd Ave. N., Grand Forks
Potter, Mrs. Wilbur F.	2024 2nd Ave. N., Grand Forks
Quale, Mrs. Victor S.	1620 Belmont Rd., Grand Forks
Ruud, Mrs. Henry O.	504½ Reeves Dr., Grand Forks
Ruud, Mrs. John E.	1404 Chestnut St., Grand Forks
Sandmeyer, Mrs. John A.	1005 Lanark St., Grand Forks
Silverman, Mrs. Louis B.	625 Belmont Rd., Grand Forks
Stratte, Mrs. Joseph J.	403 Division Ave., Grand Forks
Strom, Mrs. A. D.	Langdon
Thorgrimsen, Mrs. G. G.	1215 Lincoln Drive, Grand Forks
Tsumagari, Mrs. Y.	University Campus, Grand Forks
Turner, Mrs. Robert C.	1120 Cottonwood St., Grand Forks
Vance, Mrs. Robert W.	75 4th Ave. S., Grand Forks
Waldren, Mrs. George R.	Cavalier
Weed, Mrs. Frank E.	Park River
Witherstone, Mrs. W. H.	214 8th Ave. S., Grand Forks
Woutat, Mrs. Phillip H.	1205 Lincoln Dr., Grand Forks
Youngs, Mrs. Nelson A.	511 Reeves Dr., Grand Forks

Kolana

Craven, Mrs. John P.	409 E. 3rd Ave., Williston
Craven, Mrs. Joseph D.	915 W. 2nd Ave., Williston
Hagan, Mrs. Edward J., Jr.	410 E. 2nd Ave., Williston
Hagan, Mrs. Edward J.	410 E. 2nd Ave., Williston
Johnson, Mrs. Alan K.	1004 E. 4th Ave., Williston
Korwin, Mrs. Justin J.	701 E. 2nd Ave., Williston
Lund, Mrs. Carroll M.	701 E. 1st Ave., Williston
Pile, Mrs. Duane F.	Crosby
Skjei, Mrs. Donald	623 W. 3rd Ave., Williston
Wright, Mrs. Willard A.	822 E. 2nd Ave., Williston

Northwest

Amstutz, Mrs. K. N.	14 9th Ave. N.W., Minot
Breslich, Mrs. P. J.	818 4th St. S., Minot
Cameron, Mrs. A. L.	318 8th St. S.E., Minot
Conroy, Mrs. M. P.	821 1st Av. S.E., Minot
Devine, Mrs. J. L., Jr.	901 4th St. S.E., Minot
Ensign, Mrs. W. G.	200 11th St. S.E., Minot
Erenfeld, Mrs. H. M.	306 9th St. S.E., Minot
Erenfeld, Mrs. F. R.	616 Lincoln Drive, Minot
Fischer, Mrs. V. J.	707 3rd St. S.E., Minot
Gammel, Mrs. R. T.	Kenmare
Garrison, Mrs. M. W.	612 Mount Curve Rd., Minot
Halliday, Mrs. D. V.	Kenmare
Halverson, Mrs. C. H.	322 8th Ave. S.E., Minot
Hulit, Mrs. B. E.	320 5th Ave. S.E., Minot
Hurley, Mrs. W. C.	207 7th St. S.E., Minot
Ingals, Mrs. C. L.	435 5th Ave. N.W., Minot
Johnson, Mrs. O. W.	422 3rd St. W., Rugby
Kermott, Mrs. H. L.	Main St. S., Minot
Lampert, Mrs. M. T.	101 10th St. N.W., Minot
Pence, Mrs. J. R.	Emerson Apts., Minot
Sorenson, Mrs. A. R.	612 6th St. S.E., Minot
Sorenson, Mrs. R.	1000 4th Ave. N.W., Minot
Spomer, Mrs. J. P.	114 7th St. S.E., Minot
Woodhull, Mrs. R. B.	Thompson Apts., Minot
Wheelon, Mrs. F. E.	609 9th Ave. S.E., Minot

Sheyenne Valley

Brown, Mrs. Nida	466 4th Ave. S.W., Valley City
Crosby, Mrs. Kate	132 Central Ave. S., Valley City
Christianson, Mrs. Gunder	747 6th St. N.E., Valley City
Gilsdorf, Mrs. W. H.	222 3rd Ave. S.E., Valley City
Merrett, Mrs. J. Paul	479 3rd Ave. N.W., Valley City
Meredith, Mrs. C. J.	700 Chautauqua Blvd., Valley City
MacDonald, Mrs. A. C.	607 5th Ave. N.W., Valley City
MacDonald, Mrs. Neil A.	847 2nd Ave. N.W., Valley City
MacDonald, Mrs. Dora L.	496 Central Ave. N., Valley City
Wicks, Mrs. Fred L.	726 Chautauqua Blvd., Valley City

Sixth

Arneson, Mrs. C. A.	714 2nd St., Bismarck
Bahamonde, Mrs. Jose M.	Elgin
Baumgartner, Mrs. Carl J.	615 Washington, Bismarck
Berg, Mrs. H. Milton	214 Ave. A. West, Bismarck
Blumenthal, Mrs. Philip	501 6th St., Bismarck
Boerth, Mrs. Edwin H.	825 Griffin, Bismarck
Brink, Mrs. Norvel O.	212 Ave. F. West, Bismarck
Buckinham, Mrs. T. W.	405 Broadway, Bismarck
Cartwright, Mrs. John T.	926 7th St., Bismarck
Cochran, Mrs. R. B.	1010 Washington, Bismarck
DeMoully, Mrs. Oliver M.	Flasher
Fredricks, Mrs. Leonard H.	112 Ave. B. West, Bismarck
Goughnour, Mrs. Myron	614 6th St., Bismarck
Heffron, Mrs. M. M.	422 8th St., Bismarck
Henderson, Mrs. R. W.	1229 4th St., Bismarck
Hetzler, Mrs. A. E.	602 2nd Ave. N.W., Mandan
Icenogle, Mrs. Grover D.	232 Ave. C. West, Bismarck
Jacobson, Mrs. M. S.	Elgin
Johnson, Mrs. Paul L.	201 Ave. A West, Bismarck
Kling, Mrs. Robert R.	219 Thayer W., Bismarck
Larson, Mrs. Leonard W.	219 Ave. B West, Bismarck
LaRose, Mrs. Victor J.	522 6th St., Bismarck
Lindsay, Mrs. D. T.	1312 Mohawk, Bismarck
Nickerson, Mrs. Evelyn	309 5th Ave. N.W., Mandan
Nuessle, Mrs. Robert F.	106 Ave. D. West, Bismarck
Nugent, Mrs. Milton E.	934 Riverview, Bismarck
Perrin, Mrs. Edward D.	520 Ave. A. West, Bismarck
Peters, Mrs. Clifford H.	805 Griffin, Bismarck
Pierce, Mrs. Willard B.	615 Raymond St., Bismarck
Roan, Mrs. Martin W.	222 Park, Bismarck
Salomone, Mrs. Ernest J.	Elgin
Saxvik, Mrs. Russell O.	315 Park, Bismarck
Schoregge, Mrs. C. W.	507 6th St., Bismarck
Thompson, Mrs. Arnold M.	1124 4th St., Bismarck
Tudor, Mrs. Robert B.	714 Ave. C. West, Bismarck
Waldschmidt, Mrs. Reuben H.	600 Washington, Bismarck

Southwestern

Bowen, Mrs. Jesse W.	221 7th Ave. W., Dickinson
Dukart, Mrs. C. R.	208 4th Ave. W., Dickinson
Dukart, Mrs. Ralph J.	443 1st Ave. E., Dickinson
Guloien, Mrs. Hans E.	45 5th Ave. W., Dickinson
Gumper, Mrs. Arnold J.	7 4th St. E., Dickinson
Hill, Mrs. Simon W.	Regent
Nachtwey, Mrs. A. P.	115 5th Ave. W., Dickinson
Reichert, Mrs. Henry L.	543 1st Ave. W., Dickinson
Rodgers, Mrs. Robert W. R.	146 6th St. W., Dickinson
Smith, Mrs. Oscar M.	205 Sims, Dickinson
Spanjers, Mrs. Arnold J.	806 Park Ave., Dickinson
Spear, Mrs. Albert E.	610 1st Ave. W., Dickinson
Tosky, J.	Richardton

Stutsman

Arzt, Mrs. Philip G.	502 4th Ave. S.E., Jamestown
Beall, Mrs. John A.	501 2nd Ave. N.E., Jamestown
Carpenter, Mrs. G. S.	State Hospital, Jamestown
DePuy, Mrs. Thomas L.	301 2nd Ave. S.E., Jamestown
Elsworth, Mrs. John N.	605 5th St. N.E., Jamestown
Fergusson, Mrs. Vern D.	Edgeley
Holt, Mrs. George H.	214 2nd Ave. S.W., Jamestown
Jansonius, Mrs. John W.	405 4th Ave. S.E., Jamestown
Larson, Mrs. Ernest J.	321 2nd Ave. S.E., Jamestown
Lucy, Mrs. Robert E.	523 3rd Ave. S.E., Jamestown
McFadden, Mrs. Robert L.	910 3rd Ave. N.W., Jamestown
Maloney, Mrs. Basil W.	LaMoure
Nierling, Mrs. Richard D.	415 9th St. S.E., Jamestown
Pederson, Mrs. Thomas D.	316 4th Ave. N.E., Jamestown
Place, Mrs. B. A.	State Hospital, Jamestown
Robertson, Mrs. Clarence W.	106 6th St. N.W., Jamestown
Sommerness, Mrs. Duane	324 1st Ave. S., Jamestown
Sorkness, Mrs. Joseph	318 3rd Ave. S.E., Jamestown
Woodward, Mrs. Robert S.	310 10th Ave. N.E., Jamestown

Traill-Steele

Cahle, Mrs. Thomas M.	Hillsboro
Cleary, Mrs. H. G.	Northwood
Kjelland, Mrs. A. A.	Hatton
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LaFleur, Mrs. H. A.	Mayville
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Vandergon, Mrs. Keith G.	Portland
Vinje, Mrs. Syver	Hillsboro

Member-at-Large

Boyum, Mrs. L. E.	Harvey

Lancet Editorial

It's Our Foundation

We are all familiar with the aims, objects, and mechanics of the American Medical Education Foundation. If not, we should be, as it has been given plenty of publicity in our journals. Likewise, all of us are wholeheartedly in accord with these aims and objects — or we should be.

J. SORKNESS, M.D.

The annual report of the foundation, which came to my desk today, would indicate, however, that our support of this foundation is pitifully small as a profession — at least in this area. My first reaction was one of indignation, and the temptation was great to upbraid my professional brothers for their apparent lack of interest. Better sense prevailed, however, and I read further into the detailed report, only to find that nowhere was I credited with any part of this great work. Didn't I distinctly remember making out this check? It seemed only yesterday that I mailed this to our state secretary.

Again indignation seemed in order and better sense prevailed. I started looking through cancelled checks and nowhere could I find a record of such a check. How many of you are guilty of the same oversight?

Our lives are necessarily busy and time flies by at an inordinate rate; but we must stop, sit down, and take care of the things that are important to us. Surely, near the top of these, is the support of the schools which gave us the privilege of serving our fellow men in this difficult but soul-satisfying profession.

The goal of the foundation has not been met by half. Let us not by apathy, oversight, or carelessness fail to support it to the best of our ability. Sit down now, make out this check, and send it to the secretary of your state association. It's *our* foundation!

JOSEPH SORKNESS, M.D.,
President, North Dakota State Medical Association

Civil Defense

Civil defense is important business in which everyone is an important stockholder. The commodity of this business is protection and preservation of human life and property in the event of disaster. Each of us as stockholders must make the amount of our investment sufficient to establish and keep our organization on a sound functioning basis. This investment is our own personal time, and physical and mental energy.

Civil Defense is a complex business. No one can work in all its areas, so each individual is assigned to a job for which he has previous training or can be trained.

As an integrated part of this organization, the medical services work with and are dependent upon rescue, police, fire, communication, transportation, and many other services.

In Minneapolis, the Medical and Public Health Services, under the chairmanship of Dr. Frank J. Hill and co-chairmen Drs. Edwin G. Benjamin and Nathan C. Plimpton, have assignments for all physicians, dentists, nurses, pharmacists, and other related personnel either in first-aid units or in existing or auxiliary hospitals. In addition to skilled and already trained individuals, other volunteers who have received Red Cross training or who have previous medical experience will be assigned.

The city is divided into 11 defense zones. Each hospital or combination of two hospitals has been assigned responsibility for medical service in one of these zones. The hospitals, therefore, are an important focal point in organization of the medical services under medical leadership. A pilot study for organization of hospitals for emergency was made by Northwestern Hospital. This study, prepared by officials and staff members of the hospital and consultants, headed by Mr. Russell C. Nye, administrator, outlines a plan of operation for hospitals in an emergency. Plans are based on operation in the base or now existing hospital and in an improvised or auxiliary hospital at another location. Also, organization is moving forward for

first-aid teams in each zone staffed by professional and related personnel.

Minneapolis is a part of the state-wide medical mutual aid and mobile support plan. The Minneapolis program is integrated with the Minnesota State Civil Defense office which, in turn, is a part of the Federal Civil Defense Administration and its concern is nationwide.

Though organization may be slow, it is not static. It is a process going on daily and with full support of each member of the community, especially leadership and participation of the medical profession, the organization will meet the implication of its identification – Civil Defense.

If any physician, anywhere, has not affiliated with the Civil Defense organization of his community, he is urged to do so. If there is no Civil Defense organization in his community, he is urged to work through his local and state medical society.

E. G. BENJAMIN, M.D., *Co-chairman, Emergency Medical Service, Minneapolis Civil Defense*

Congenital Dysplasia of the Hip Joint and Sequelae in the Newborn and Early Postnatal Life, by VERNON L. HART, M.D., F.A.C.S., assistant professor of surgery, University of Minnesota, editor, ROBERT P. KELLY, M.D., 1952. 187 pages. Springfield, Illinois: Charles C Thomas, $5.00.

A chronological review of the history and development of modern concepts of congenital hip dysplasia plus diagnosis and treatment is presented.

Methods and importance of early diagnosis is emphasized. Numerous photographs and illustrating x-rays are used.

Though there is considerable repetition, the facts presented are imperative knowledge for all physicians.

D.K.H.

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Synopsis of Pathology, by W. A. D. ANDERSON, M.D., professor of pathology, Marquette University School of Medicine; pathologist, St. Joseph's Hospital, Milwaukee, Wisconsin. Edited by the C. V. Mosby Company, St. Louis, Mo., 1952. Third edition, 787 pages, Price $8.00.

The third edition of this well-known synopsis follows the pattern established by the previous two editions but shows numerous revisions and the addition of certain recently described or publicized pathological changes such as the L. E. phenomenon in disseminated lupus erythematosis, beryllium granulomatosis, and the vascular changes of thrombotic thrombocytopenic purpura. The discussion of each disease is clear and as complete as can be expected in a synopsis. The photographic illustrations are for the most part good. The book admirably fulfills its function as a resume of the major pathological changes found in association with all well known pathological processes. References are limited but adequate and up to date. The book is of little value to the trained pathologist but of great value to the medical student just learning the fundamentals of pathology and to the clinician who wishes a short, concise idea as to the pathological processes associated with the various clinical entities with which he is familiar.

J.I.C.

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Neurosurgery: An Historical Sketch, by GILBERT HORRAX, M.D., Sc.D., Chief of Neurosurgical Service, the Lahey Clinic, 1952. 142 pages, 69 illustrations, 181 references. Springfield, Illinois, Charles C Thomas.

The author describes in a short, concise, chronological order the development of the field of neurosurgery, with its evolution from prehistoric times, as evidenced by the trephined skulls found, to the present day.

He shows us how the indications for surgery, techniques, and prognoses have progressed; the strides made since the development of anesthesia, aseptic techniques, and cerebral localization; and finally, the development of the field of neurosurgery as a specialty. The outstanding workers in the field of medicine are quoted briefly and liberal references listed, indicating extensive research on this subject. P.

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Practical Blood Grouping Methods, American Lecture Series, by ROBERT L. WALL, 1952, Springfield, Illinois: Charles C Thomas $5.00.

In its treatment of subject matter, this book is directed principally toward fulfilling the needs of workers concerned directly with blood banking. It handles extensively and well all manner of laboratory techniques in blood banking, including those of blood typing, cross-matching, dilution titration tests, and the use of the Coombs test. The immunological principles involved are dealt with in a concise and lucid manner.

In the 15 years since blood banking came into existence, knowledge has advanced with amazing rapidity. These years have seen the discovery of the Rh factors and a concept of their clinical importance; discovery of seven other blood group systems; developing awareness of the physicochemical properties of the antigen-antibody reaction; isolation and use of blood-group specific substances, and many other technical achievements. Blood banking techniques, under the pressure of these developments, have undergone a gradual evolution, providing continuously more certain approval of blood for transfusion.

In the light of these circumstances, this book is indeed timely. It will provide aid to the laboratory technologist who feels lost in this wave of technical advance. Many physicians will find it helpful in understanding problems in a complex field.

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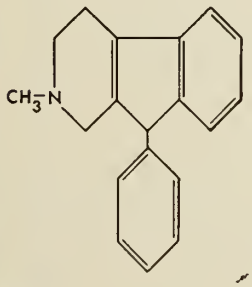

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*References on request

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News Briefs . . .

North Dakota

THE following 32 physicians have been licensed to practice in North Dakota as a result of the July examination of the State Board of Medical Examiners:

Stuart John Cook, Roland, Manitoba; Richard Joseph Zauner, Fargo; Martin Alexander Platsko, Edmore; Dean R. Strinden, Litchville; John S. McArdle, Minot; Gordon Earl Ellis, Fargo; John Francis Connor, Winnipeg, Manitoba; Maynard B. Gustafson, Fargo; John Donald Thordarson, Maddock; Roger M. Berg, Bismarck; Gestur Kristjansson, Bottineau; Nicholas Gus Boosalis, Englewood, Colorado; Paul Vincent Coldrey Adams, Langdon; Fred Fokke Veenbaas, Winnipeg, Manitoba; Nevine Wright Turner, LaMoure; Jens Sahl, Jr., Minot.

Paul Frederick Chirstenson, Jamestown; Harris D. Hanson, Fargo; Herbert Joslin Wilson, Elbowoods; Paul Jule Beithon, Wahpeton; Rudolph P. Froeschle, Tioga; James A. Leigh, Grand Forks; Keith G. Foster, Dickinson; Robert E. Hankins, Mott; Peter Roy Gregware, Bismarck; James Marr, Grafton; James M. VanderLinde, Jamestown; Andrew Gerhard Sathe, Fargo; Donald Lee Carlon, Fargo; Robert A. Kyle, Bottineau; Robert H. DeLano, Northwood; Wendell W. Wall, Wahpeton.

* * *

A NEW CLINIC designed to provide emergency facilities for two physicians and a dentist is expected to open in Tioga in November. The $30,000 building will be the first step in Tioga's hospital program.

* * *

A FREE summer camp for diabetic children ran from August 9 through 16 at Turtle River State Park. This is the first camp of its kind in North Dakota, but it will probably become an annual event. Physicians required by the camp furnished their services free of charge.

* * *

DR. THEODORE H. HARWOOD, Vermont physician and educator, has been named dean of the University of North Dakota school of medicine. Dr. Harwood succeeds Dr. W. F. Potter who resigned June 11. Dr. Potter will be retained on the medical school staff as head of the department of physiology.

* * *

THREE physicians have been appointed by Governor Brunsdale to three-year terms as members of the State Board of Medical Examiners. The appointees are: Dr. O. W. Johnson, Rugby; Dr. H. L. Reichert, Dickinson; and Dr. Joseph Sorkness, Jamestown.

* * *

DR. GEORGE L. LOEB, superintendent of the North Dakota State Tuberculosis Sanatorium at San Haven, has been reappointed to that position by the State Board of Administration.

* * *

DR. JAMES J. MOSES, a member of the medical staff of the Quain and Ramstad Clinic in Bismarck for the past year, opened a practice in Richardton on August 1.

* * *

THE University of North Dakota medical school has been awarded a grant of $9,285 by the National Fund for Medical Education. This grant is one of 79 awarded to each of the 73 four-year medical schools and 6 to the two-year schools, totaling $1,944,151.64.

* * *

DR. R. P. FROESCHLE, formerly of Sparta, Wisconsin, has opened an office in Tioga. Dr. Froeschle is the first resident physician Tioga has had since the early 1930's.

DR. LLOYD S. RALSTON, formerly of Grand Forks and Larimore, has returned to Grand Forks and joined the staff of the Grand Forks Clinic, which brings the number of doctors on the staff to 19.

Minnesota

ATTENDANCE at medical short courses at the University of Minnesota's Center for Continuation Study increased 19 per cent during the 1952-1953 academic year. The annual report of Dr. Robert B. Howard, director of continuation medical education at the university, showed that more than 1,000 Minnesota physicians participated in the courses. Another 566 doctors attended homecoming clinics, doctors' days, and a special symposium on metabolism of potassium.

* * *

The Owen H. Wangensteen Surgical Education Foundation has been established at the University of Minnesota to promote advanced surgical education. Initial funds were donated by Dr. F. John Lewis, associate professor of surgery; Dr. Richard L. Varco, professor of surgery; and Dr. Charles E. Rea, clinical associate professor of surgery. Dr. Wangensteen will act as an adviser in administration of the funds.

* * *

DR. CHARLES W. MAYO of the Mayo Clinic, Rochester, was nominated by President Eisenhower on July 27 to be an alternate delegate to the eighth session of the United Nations general assembly. The assembly is scheduled to meet September 15.

* * *

A GRANT of $15,000 from the Damon Runyon Memorial Fund for Cancer Research has been given to Dr. Owen H. Wangensteen, chief of surgery at the University of Minnesota medical school and hospitals. Dr. Wangensteen will use the funds to restudy operations on patients suffering from gastric, colic, and rectal cancer.

* * *

DR. L. EARLE ARNOW has been appointed a vice president of the Sharp and Dohme Division of Merck. Joining the organization in 1942 as director of biochemical research, he became director of research two years later. Prior to that he was assistant professor of physiological chemistry at the University of Minnesota Medical School.

South Dakota

ABOUT 500 persons attended an open house tour recently at Methodist State Hospital, Mitchell, to celebrate completion of the renovation program which was started October 1, 1951. Total cost was $525,000, of which the federal government paid $170,000. Included in the renovation project was the construction of a complete fourth floor housing surgery, laboratory, and central supplies.

* * *

DR. A. W. SPIRY of Mobridge, was named president-elect of the South Dakota Medical Association at its annual convention in Rapid City recently. He will automatically become president of the group in a year. Other officers elected were: Dr. Floyd Gillis, Mitchell, vice president; and Dr. G. I. Cottam, Sioux Falls, secretary-treasurer.

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American College Health Association News . . .

The Executive Committee has selected the Broadmoor hotel, Colorado Springs, for the 1955 annual meeting. The dates are April 28, 29, and 30. The Rocky Mountain Section will act as hosts for the meeting.

* * *

The American College Health Association has been invited to send a delegate to the Fourth National Conference on Physicians and Schools to be held in Illinois in October 1953. The general conference theme will be "Health Services for School Children." More than 50 nationally known leaders in school health will serve as consultants.

Dr. Leona B. Yeager, director of student health service, Northwestern University, Evanston, Illinois, will represent the association at this meeting. The conference, sponsored by the American Medical Association and conducted by its Bureau of Health Education, will be the fourth of a series, the first of which was held in 1947, the second in 1949, and the third in 1951. The conferences serve as an exchange of information on school health services, a means of establishing policies to promote and extend health services for all school children, and a method to stimulate joint action of public health, educational, and medical professions leading to the development of sound school health services.

* * *

The Department of Health of the Woman's College of the University of North Carolina moved into the new infirmary in June. Dr. Ruth M. Collings, director of the department, reports that both the clinic calls and the infirmary admissions show a pronounced increase during the past academic year over those of the previous year.

* * *

Changes in staff: Mrs. Hazel DeTrude, R.N., is director of health service, Baldwin-Wallace College, Berea, Ohio.

Dr. Charles J. Hutchinson replaces retiring Dr. Charles A. McDonald as director at Brown University, Providence, Rhode Island.

Mrs. Juanita Hawk, R.N., is the new director at Oklahoma City University.

Dr. Dock Curtis, who has just completed a residence in student health at Cornell University, is replacing Dr. Helen M. Deane, associate physician at the Woman's College of the University of North Carolina.

* * *

Dr. Max L. Durfee, director of health service at Oberlin College and immediate past president of the association, is assisting the Milwaukee Health Department during the summer.

Dr. Durfee has accepted the chairmanship of the Tuberculosis Committee for this year.

* * *

A major purpose of this column is to serve as an exchange of information on programs and activities which the college health services are carrying out or planning as well as news of personnel. The effectiveness of this column depends largely on the material submitted by every college health service. It is hoped that news and information will be mailed regularly to the secretary of the American College Health Association.

The Journal Lancet

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

Diabetic Retinopathy*

ROBERT R. COOPER, M.D.

Minneapolis, Minnesota

THE PRESENCE of retinal pathology in association with diabetes mellitus has been recognized for many years. A comprehensive analysis and description of this condition has not, however, been forthcoming until the past decade when the work of Wagener, Friedenwald, and Ballantyne (and several others) has been reported and the entire picture which we know as diabetic retinopathy somewhat clarified. While the etiological factors responsible for the retinal lesions are not yet clear, our knowledge of the histology and pathology of these lesions has advanced greatly in the past few years, and we are now able to recognize this condition in a much earlier and insidious stage than was possible before. The visual changes which can be produced by diabetes may vary from a barely noticeable disturbance to a profound intraocular disease terminating in total blindness. It is obviously of the greatest importance that we look for these retinal signs in any patient with diabetes and be constantly aware of this serious complication.

Diabetic retinopathy was not recognized as a separate entity for many years after it was first described. Its similarity to the retinitis of hypertension and arteriosclerosis is probably responsible for this. In 1921, the statement was made by Wagener and Wilder that the "retinopathy of diabetes is essentially the retinopathy of arteriosclerosis." This concept was accepted for some time until further investigation revealed that diabetic retinopathy was an entirely separate condition when seen in its pure form. It is now universally felt that a differentiation between diabetic and hypertensive retinopathy can be made clinically and pathologically in nearly every case.

Since the discovery of insulin and with the modern methods of treating diabetes, the incidence of diabetic retinopathy has increased markedly—especially in the younger age group. Wagener, in his studies at the Mayo Clinic, found retinopathy in 8.3 per cent of diabetics in 1921, while 30.6 per cent of diabetic patients showed typical retinal findings in 1945. It has been found that the duration rather than the severity of the diabetes is the determining factor in the development of retinopathy. This fact is brought out by the following table (from Wagener):

Known duration of diabetes	*Per cent of cases showing retinopathy*
Less than 1 year	10.7
1 to 10 years	22.0
11 to 15 years	65.0
More than 15 years	67.0
More than 20 years	73.0

Dolger has recently observed that all of 200 "well controlled" cases who had had diabetes for a period of 25 years exhibited signs of vascular

ROBERT R. COOPER *was graduated from the University of Minnesota in* 1946, *specializes in ophthalmology in Minneapolis, serves on the staffs of Fairview, Swedish, and Deaconess hospitals, and as clinical instructor in ophthalmology at the University of Minnesota medical school.*

*Presented at the medical staff conference of the Minneapolis Veterans Hospital, Minneapolis, Minnesota.

disease—it is presumed that this was also evident in the retina, since retinopathy is usually one of the earliest signs of diabetic vascular disease. Females are more commonly afflicted with diabetic retinopathy than males in a percentage ratio of 84 to 16. The average duration of known diabetes before the onset of retinopathy is 19 years in males and 10 years in females. It is well known that typical diabetic retinopathy may be found in a patient with no clinical signs of diabetes, a normal blood sugar, and perhaps only a moderately elevated glucose tolerance curve; such a patient will almost invariably develop diabetes at some later date.

In a patient with clinical diabetes, proper control of the blood sugar level does not preclude against the development of retinopathy, and the retinal lesions are seen with equal frequency in patients who have been adequately controlled and in those whose management has not been satisfactory. An exception to this statement has been taken by Spoont, Dyer, Day, and Blazer who in a recent evaluation of 50 cases felt that there was a significant difference in the percentage of diabetic patients exhibiting retinopathy in two groups of cases—one group "well controlled" and the other "poorly controlled." In their study, however, it is made apparent that the "evaluation of the degree of diabetic control is difficult," and we must therefore reserve our opinion of this factor until more accurate means of evaluating diabetic control are available. The retinopathy after it has developed will not necessarily regress with careful control of the blood sugar level. It is felt that the development of retinopathy is due to some factor inherent in the diabetes itself rather than to the blood sugar level or extraneous vascular or infectious processes. Extraneous vascular disease or chronic infections may, however, increase the severity or the rapidity of development of retinopathy.

RETINAL PICTURE

The funduscopic picture of diabetic retinopathy is characterized by microaneurysms, hemorrhages, exudates, and venous changes with a normal appearance of the arterioles. If arteriolar changes are present, we are dealing with a mixed type of retinopathy. The typical diabetic changes are usually found between the superior and inferior temporal vessels and extending to the region of the optic papilla; however, in more advanced cases, these lesions will be seen to involve a greater area and may extend to the most peripheral portions of the retina.

The earliest and most characteristic finding is the microaneurysm. These are minute, punctate red spots of approximately 50 to 60 micra in diameter. They are round, globular, and may sometimes be accentuated by a bright central reflex when viewed with the ophthalmoscope. These microaneurysms will be seen to remain essentially unchanged for many months in contrast to the fleeting nature of the punctate hemorrhages seen in arteriolar disease. These lesions may be present in the retina before any other clinical signs of diabetes have appeared, except for a slight elevation of the glucose tolerance curve in certain cases.

Retinal hemorrhages are also seen and may vary from tiny flame-shaped spots to larger "blots." These extravasations are related to rupture of a microaneurysm or result from diapedesis of red cells through the aneurysmal wall. The hemorrhages are usually limited to the posterior portion of the globe and are not generally as widespread as the microaneurysms. In far advanced cases, however, they too may be found in the peripheral retina.

Exudates are frequently seen surrounding the capillary aneurysms. These are of the "waxy" or "hard" type and are also seen more frequently in the central portion of the retina. They usually begin as small discrete areas which gradually coalesce to form larger patches. The margins of the exudates are typically sharp and distinct, and they vary from white to light yellow in color. Cotton-wool patches or "soft" exudates are not characteristically seen in diabetic retinopathy, and when present are indicative of a toxic process superimposed on the diabetes. They are seen in a mixed type of retinopathy when there is obvious arteriolar disease, hypertensive or arteriosclerotic in type.

Venous changes have long been recognized as an accompaniment of diabetic retinal disease. Nettleship in 1888 described dilatation and beading of the retinal veins in a patient with diabetes, and it was thought for many years that this was the most typical finding in diabetic retinopathy. This, however, is not as common as the microaneurysm previously described. The veins, when involved, show a dilatation and increased tortuosity, which is not necessarily evident in all their branches. The affected vessel may show beading and may double back on itself forming loops and "horseshoes." New vessel formation may be evident, and the vessels may project above the retina into the vitreous. If the new vessels do rise into the vitreous, a gross vitreous

hemorrhage frequently occurs and retinal detachment usually follows. The simple dilatation of a retinal vein is rarely accompanied by retinal hemorrhage which serves to distinguish it from a branch venous occlusion.

PATHOLOGY AND PATHOGENESIS

For a considerable period of time after the characteristic punctate red spots were first described, they were considered to be minute hemorrhages identical with those seen in arteriolar disease. It remained for Friedenwald and Ashton to demonstrate conclusively that they were true capillary aneurysms. This work was further substantiated by Ballantyne. Histologically, these aneurysms appear "as mulberry-like bodies composed of a compact mass of erythrocytes enclosed in a membrane of varying thickness" (Ballantyne). The connection with their parent capillaries has been demonstrated in several instances. In pathological section, swelling of the capillary endothelial cells has been noted causing partial or complete blockage of the vessel. Two factors have been considered in the formation of these aneurysms: (a) weakening of the resistance of the capillary walls (from swelling of endothelial cells), and (b) a relative increase of pressure within the vessel. The reason for this "capillary hypertension" is not known. It may be that the reduced intraocular pressure resulting from variations in blood sugar level is also a factor in the formation of these aneurysms. This theory has recently been advanced by Ashton, but has not as yet been substantiated. It is interesting to note that microaneurysms have not been demonstrated in any organ in the body except the retina. This leads us to believe that there is an anatomic peculiarity of the retinal capillaries predisposing them to such lesions, or that there is in diabetic patients a specific substance toxic to the retinal capillaries and not to the capillaries of the other organs.

As mentioned previously, the retinal hemorrhages frequently seen are usually associated with rupture of a microaneurysm. Since the aneurysms are characteristically found in the inner nuclear layer of the retina, the hemorrhages are limited for the most part to this zone. Consequently, they do not usually exhibit the striated or "flame-shaped" appearance of the hemorrhages seen in arteriolar disease where the extravasation occurs in the retinal nerve fiber layer. This rupture of the aneurysmal wall is probably due to two causes: the first being a weakness in the capillary wall from swelling of the endothelial cells, and secondly because of "prestasis" or slowing of blood flow through the dilated terminal vessels (Ricker). It is to be remembered in this connection that capillary fragility is increased in nearly all patients with diabetic retinopathy, regardless of whether they exhibit hypertension or not. The cause of dilatation of the terminal vessels is not known for sure, but Elwyn feels that prolonged hyperglycemia is a factor.

The hard exudates usually seen in the immediate vicinity of an aneurysm are composed of colloid or hyaline material. These are usually located in the outer fibrillary layer and are formed by leakage of plasma from the aneurysmal wall and the adjacent capillary net. The exudates are due to a chronic state of subnutrition and poor oxygen supply secondary to slowing of the blood flow through the capillary bed.

The venous changes are due to a retinal phlebosclerosis. This has further been divided into three types—intimal, medial and adventitial (Gibson and Smith). Of these, the medial type is the most common. This sclerosis may be evident in several forms—there may be simply a generalized dilatation and tortuosity accompanied by beading of the smaller branches, or there may be marked tortuosity with loop and coil formation. In more severe involvement, there may be proliferation of the venous tree with new vessel formation. In some instances, this neo-vascularization may extend into the vitreous resulting in massive vitreous hemorrhage, retinitis proliferans and retinal detachment. In certain cases, it is felt that venous stasis may occur before the appearance of microaneurysms; it is not uncommon to see dilated retinal veins in diabetic patients who do not exhibit ophthalmoscopic signs of diabetic retinopathy. It is important to remember that varices in the retina are rare except in association with diabetes.

DIFFERENTIAL DIAGNOSIS

As mentioned in an earlier paragraph, the retinopathy of diabetes was once thought to be identical with that of arteriosclerosis and hypertension (not associated with diabetes). The main differential diagnosis, then, lies between these conditions. The retinopathies of diabetes and hypertension are separate entities, both clinically and histologically. In each, the earliest changes are seen in the retinal vessels—in diabetes, the venous side of the circulation is involved, and in hypertension the arterial side. The finding of microaneurysms, exudates, and venous congestion in the presence of normal arterioles leads us immediately to suspect diabetes. If arteriolar pathology is found concomitantly with the above signs, we are dealing with a

mixed type of retinal vascular disease. The retinal hemorrhages seen in diabetes occur primarily in the deeper layers and therefore are irregular in shape, while in hypertensive retinopathy the extravasations are in the nerve fiber layer and consequently have a striate or flame-shaped appearance. The soft exudate or "cotton-wool" patch so frequently seen in arteriolar disease does not occur in diabetes unless there is an associated toxemia. Of course, in certain cases, the systemic manifestations of the disease must be taken into consideration in order to properly evaluate the ophthalmoscopic picture—this applies especially to the very early stages of a mixed type of retinopathy.

The relationship of diabetic retinopathy to intercapillary glomerulosclerosis (Kimmelstiel-Wilson's disease) has long been a subject of controversy. Ashton feels that these conditions are both manifestations of the same pathological process modified by the different anatomical structure of the retinal and glomerular vessels. The retinal lesions probably precede the renal disease. At any rate, the simultaneous occurrence of these two conditions leaves little doubt that they are in some way related.

TREATMENT

Therapy directed at the prevention or abolition of diabetic retinopathy has been universally disappointing. As mentioned previously, proper control of the blood sugar level does not seem to alter the course of the retinal disease appreciably, and after retinopathy appears, it does not as a rule regress even though the diabetes is adequately controlled.

There is recent evidence that there may be some retardation of the process in a significant number of cases who are maintained on a controlled diet rather than the "free diet" regime which was advocated by some investigators. While relatively normal vision may be maintained for many years, the complete abolition of the retinopathy is rarely, if ever, achieved.

Because of the increased capillary fragility seen in these cases, numerous attempts have been made to improve the retinal disease by decreasing the capillary fragility. Vitamin C with and without B-complex has been used with no success. Hesperidin (vitamin P) has been found to reduce capillary fragility, but the retinal pathology has not been affected appreciably.

Because of the sex distribution and the longer duration of known diabetes before the onset of retinopathy in males, Saskin, Waldman, and Pelner have used male hormones in the treatment of these cases. Testosterone was given intramuscularly in a series of unselected diabetics showing retinal disease. In their series, definite improvement in retinopathy was noted in over 40 per cent of cases. No improvement in visual acuity was demonstrated. This treatment will merit further consideration and investigation.

It is generally agreed that the factors responsible for the development of diabetic retinopathy are closely related to or identical with those factors which produce diabetes itself. The final answer to the treatment of this eye condition then will depend upon our progress in treatment of the primary disease.

SUMMARY

1. A brief discussion of the incidence of diabetic retinopathy and its relationship to the duration of known diabetes has been given. It was emphasized that the percentage of diabetic patients exhibiting retinal pathology is steadily increasing, especially in the younger age group.

2. The ophthalmoscopic picture of diabetic retinopathy was described and the pathology and pathogenesis of the characteristic lesions briefly discussed. The most characteristic and usually the first sign of diabetes in the retina is the microaneurysm, although venous dilatation may in some cases occur first.

3. The differential diagnosis of diabetic and hypertensive retinopathy was mentioned. It is important to remember that in a pure case of diabetic retinopathy, the arterioles will appear normal ophthalmoscopically.

4. Treatment of this condition is discussed very briefly since there has been little if any success in attempting to prevent or abolish diabetic retinal disease. The recent use of testosterone is mentioned, but there is as yet insufficient evidence to properly evaluate its effect in this disease.

5. The ocular manifestations of diabetes other than retinopathy have deliberately been excluded from this discussion since they do not properly fall within the scope of this paper.

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Radioactive Iodine in the Diagnosis and Treatment of Thyroid Disease*

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The discovery of artificial radioactivity was made by Joliot and Curie in 1934. Fermi,[1] also in 1934, described the first radioactive isotope of iodine, I^{128}. Hertz, Roberts, and Evans[2] used radioiodine in physiological studies and noted the marked avidity of the thyroid gland for iodine. Hertz and Roberts[3] first used radioiodine in the treatment of hyperthyroidism in 1941. In 1940, Hamilton and co-workers[4] made the first attempt to localize radioiodine in thyroid carcinoma without success. Seidlin and associates,[5] in 1946, were able to demonstrate uptake of radioiodine in a metastasis from thyroid carcinoma and treated this lesion with I^{131}. Since the early work by Hertz in 1938, an enormous literature has accumulated describing the studies with radioiodine by numerous investigators on the physiology and disease states of the thyroid gland. Radioiodine is an ultra sensitive and simple means of studying complicated biological and chemical systems.

THE PREPARATION OF RADIOACTIVE IODINE

Until 1946 it was necessary to produce radioactive iodine in the cyclotron, a laborious process yielding only small quantities of the various isotopes. Studies with radioiodine were thus restricted to a few large centers with access to a cyclotron. In 1946 large quantities of radioactive iodine became available to qualified investigators through the large scale production of radioisotopes at Oak Ridge National Laboratories. This has greatly stimulated both clinical and physiological studies with radioactive iodine.

Fourteen radioactive isotopes of iodine have been identified, but only four are used to any extent in research, diagnosis, or treatment. The first radioisotope of iodine identified was I^{128} which has a half life of 25 minutes. By 1940, I^{130} (half life 12.6 hours), I^{126} (half life 13 days), and I^{131} (half life 8 days) had been identified and were being used experimentally. Gradually, I^{131} has become the main isotope in general use because of its desirable rate of decay and the ease and abundance with which it can be produced.

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In the cyclotron, I^{131} is prepared by bombarding tellurium with deuterons. At Oak Ridge I^{131} is produced in the chain reacting uranium pile by either of two processes. In the fission of uranium 235, two fragments are formed. One of the fragments is Sn^{131} (tin) which goes through several stages of beta decay until stable Xe^{131} (xenon) is formed. At one stage in this process of decay, I^{131} is formed and can be chemically isolated for use. I^{131} may also be prepared by the bombardment of stable tellurium (Te^{130}) with slow neutrons in the atomic pile with the production of Te^{131} (half life 1.2 days). Te^{131} decays by beta emission into I^{131}. The I^{131} regardless of the method of its production decays into stable xenon, each atom of I^{131} emitting one beta particle (maximal energy .595 Mev) and two gamma rays (maximal energy .360 Mev). Its therapeutic effect and also its ability to be traced and measured with a Geiger-Muller counter is due to these nuclear radiations.

The radioactive iodine is chemically separated and purified as carrier free I^{131}. It contains only tracer amounts of tellurium. The carrier free I^{131} is actually only a very minute amount of iodine. One millicurie of I^{131} weighs only .008 micrograms. This is of importance since in the dosage range generally used it can be certain that the effect obtained is due to radiation rather than to the effect of the iodine itself.

Radioactive iodine is identical in its biological and chemical properties to stable iodine I^{127}. The chemical identity of radioactive iodine and stable iodine is demonstrated by several observations. Under appropriate conditions exchanges to theoretical equilibrium can be observed between radioiodine and diiodotyrosine and vice versa. When physiological experiments are performed using radioactive and chemical methods for iodine in parallel, good agreement is observed. And finally, administered radioactive iodine appears in diiodotyrosine and thyroxine in the thyroid gland and the protein bound fraction of the serum.

THE FATE OF RADIOACTIVE IODINE IN THE BODY

Marine and Feiss[6] in 1915 first demonstrated in perfusion experiments that the thyroid was the only tissue that took up significant amounts of iodine.

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They observed the great affinity of normal thyroid tissue for iodine, and particularly the avidity of hyperplastic thyroid tissue which was low in iodine content. Hamilton[4] pointed out that thyroid tissue has the capacity of concentrating iodine to 10,000 times the blood level. This thyroid to blood ratio is increased in a hyperplastic gland. There is, however, a limit to the total quantity of iodine the thyroid can concentrate, and as larger and larger amounts of iodine are administered the thyroid/blood gradient falls. The normal thyroid requires about 50 to 100 micrograms of iodine daily for synthesis of hormone. Even a hyperplastic gland requires no more than 200 to 250 micrograms daily, since iodine from degraded hormone is reused for hormone synthesis. Thus it is apparent that adding large amounts of stable iodine as carrier for radioactive iodine will cause saturation of the thyroid gland, and give a falsely low impression of the gland's avidity for iodine.

Only very small quantities of iodine are taken up by body tissues other than the thyroid gland. Rall[7] reported the tissue distribution of I^{131} in a patient with metastatic thyroid carcinoma who was given 63 millicuries of I^{131} 56 hours before death. At autopsy only minute quantities of radioiodine were found in tissues other than functioning thyroid tissue. The irradiation to each tissue was calculated as 12 R.E.P. per day per microcurie per gram of tissue. The distribution of radioactive iodine in this patient, and the irradiation to his tissues are shown in table I. Trunnell[8] reported the distribution of I^{131} in nine autopsied patients who had been given large doses of radioactive iodine before death. He felt that with large dosage (100 millicuries or more) significant irradiation was given to the adrenals, bone marrow and other vital organs, although in comparison to the irradiation to the thyroid, this was quite small. In animal experiments the parathyroid glands have been found to take up negligible amounts of radioactive iodine. Gorbman[9] estimated that the minimum thyroid lethal dose of I^{131} was in the range of 120,000 R.E.P. Studying mice he found that tissue in the thickest portion of the gland was the first to be destroyed, and the apices and isthmus were the last to be destroyed. With large doses of I^{131} the thyroid gland was replaced by a dense fibrous scar within two weeks. Very large doses were necessary to cause injury to the parathyroids and recurrent laryngeal nerve, however much less was necessary to destroy the thymus gland. A transient loss of tracheal epithelium occurred frequently, and in a few mice nodular fibrous tumors involving the trachea were found. About eight months after administration of thyroid lethal doses, 90 per cent of the mice developed a noninvasive, expanding, chromophobe tumor of the anterior pituitary, which caused death by pressure. The dosage of radioactive iodine used in this experimental work would be equivalent to doses of 210 to 3500 millicuries in a 70 kilogram human, or 10 to 175 times the usual maximum dosage used in the treatment of hyperthyroidism. Goldberg and Chiakoff[10] reported the occurrence of malignant thyroid tumors and multiple adenomas in 2 of 10 rats, 18 months after administration of 400 microcuries of I^{131}. Quimby and Werner[11] sent questionnaires to 70 radiologists and 31 thyroid specialists in an attempt to determine the incidence of thyroid carcinoma following deep x-ray therapy to the thyroid gland. They concluded that late carcinoma of the thyroid gland following deep x-ray therapy was rare if ever occurring.

TABLE I

DISTRIBUTION OF RADIOACTIVE IODINE IN THE TISSUES OF A HUMAN GIVEN 63 MILLICURIES OF I^{131} 56 HOURS BEFORE DEATH*

Organ	I^{131} in percent of dose administered	Total tissue dose in R.E.P.
Thyroid	20	181,000
Pituitary	under 0.1	158
Testes	under 0.1	6
Adrenals	under 0.1	4
Pancreas	under 0.1	7
Red marrow	3	182
Brain	2	130
Liver	3.9	274
Kidneys	under 0.1	22
Muscle	3.3	6
Spleen	under 0.1	6
Stomach and G.I. tract	2	75
Bladder	0.1	76
Blood and extracellular fluid	1.7	—
Urine	69.1	—
Feces	2	—

*From Rall et al., J. Clin. End. 9:1379, 1949

Hertz[2] and Hamilton[4] found that radioactive iodine is rapidly absorbed in the stomach and can be detected in the hand within three to six minutes after oral administration. Absorption in the stomach is 75 per cent complete in one hour and apparently complete in three hours. Only a small amount of radioiodine is excreted in the stool, usually not more than 3 per cent and never more than 11 per cent. McConahey[12] found that the concentration of radioiodine in the blood rises to a maximal level within one hour after oral ingestion. In analyzing the curve of total blood iodine after oral administration of I^{131}, three components were revealed: first, a rapid rise to maximal concentration and a brief rapid fall, reflecting the absorption from the G.I. tract and the establishment of an equilibrium between blood and body fluids; then a more prolonged fall at an exponential rate, reflecting the disappearance of radioiodine as inorganic iodide from the blood and body fluids into the urine, thyroid tissue, and other sites of disposal; finally a continued but much slower fall, reflecting the appearance of organically bound radioactive iodine in the blood.

THE METABOLISM OF IODINE BY THYROID TISSUE

The only two organs in the human body which compete for iodine are functioning thyroid tissue and the kidneys. What is not taken up by the thyroid is excreted by the kidneys. The metabolism of iodine by the thyroid gland can be divided into three phases: the accumulation of iodine by the gland, the synthesis of thyroid hormone, and the secretion of thyroid hormone. Iodine accumulation consists of two stages, the trapping of inorganic iodide out of the plasma, and the conversion and storage of this trapped iodide as organically bound iodine. The trapping process is the rapid concentration by the thyroid of large quantities of circulating iodide, apparently in the follicle cells. If the trapped iodide cannot be utilized for hormone synthesis, most of it passes out of the thyroid within 24 hours. After being trapped by the gland, the inorganic iodide is rapidly converted to organically bound iodine and stored as diiodotyrosine and thyroxine in the colloid of the follicles. This converted, organically bound iodine accounts for more than 90 per cent of the thyroid I^{131} 48 hours after administration of the tracer dose. Organically bound I^{131} has been demonstrated in the follicular epithelium and colloid of rat thyroids as early as 30 minutes after giving a tracer dose. By 24 hours after the administration of the tracer dose, all the organically bound iodine is found in the colloid, indicating that the follicular epithelial cells probably convert iodide to organically bound iodine. It has been demonstrated that the trapping of iodide is distinct and separate from the conversion of iodide to organically bound iodine.[13–17] Rat thyroids, in which hormonal synthesis has been blocked by thiouracil, are still capable of trapping large quantities of inorganic iodide. Thiocyanate, which inhibits the collection and trapping of iodide by the thyroid, causes a rapid discharge or inorganic iodide from the gland, but does not cause the release of organically bound iodine.

Thyroid tissue contains iodine in only three chemical forms: inorganic iodide (less than 10 per cent), thyroxine (about 25 per cent), and the remainder as diiodotyrosine (about 65 per cent). It is thought that thyroxine and diiodotyrosine form the protein molecule of thyroglobulin, and that diiodotyrosine is the precursor of thyroxine, the active thyroid hormone.

A great deal of interest is centered on the mechanism of the effect produced by various antithyroid drugs. Thiocyanate has been shown to block the trapping of iodide by the thyroid, and leads to hypertrophy of the thyroid gland with formation of a goiter, sometimes associated with myxedema.[13–15,18] The thioureas and sulfonamides block the synthesis of thyroid hormone and do not affect the trapping of iodide by the thyroid gland.[13,14,16,17] Iodine in large amounts is thought to inhibit conversion of iodide to organically bound iodine, and thus have an involuting effect on the thyroid gland. Certain foods (cabbage, rutabaga, soy beans, etc.) have been shown to be goitrogenic if given in very large amounts.[19]

It has been shown that thyrotropic hormone secreted by the anterior pituitary causes the thyroid to have an increased avidity for iodine and also an increased rate of formation and secretion of thyroid hormone. Hypophysectomy greatly depresses all three thyroid processes.[20,21] Keating[22] found in chicks that thyrotropic hormone caused a rapid loss of hormonal iodine from the thyroid and hypertrophy of the gland, but that the increased iodine avidity was a secondary result and not due to any specific effect of thyrotropin on the collection of iodide by the thyroid. It has been recently shown that thyrotropic hormone in addition to its affect on thyroid iodine accumulation also causes an increased rate of release of thyroid hormone.[23] ACTH and cortisone, administered to humans with normal thyroid and adrenal function, causes a depression of the serum protein bound iodine and the thyroid uptake of radioactive iodine.[24] It is thought that this is due to depression of the anterior pituitary because of the high level of circulating adrenal steroids. Depression of the thyroid I^{131} uptake has also been demonstrated in rats receiving ACTH and cortisone.[25]

THE USE OF RADIOIODINE IN THE DIAGNOSIS OF THYROID DISORDERS

It has been established in both experimental animals and in humans that in hyperthyroidism there is an increased avidity of the thyroid gland for iodine, and in myxedema the iodine uptake by the gland is greatly decreased. The level of protein bound iodine in the blood also varies directly with the functional state of the thyroid gland. It is high in hyperthyroidism and low in myxedema, and reflects the quantity of thyroid hormone being produced and secreted by the thyroid. The renal excretion of iodine is a reflection of the thyroid uptake and varies inversely with the thyroid uptake. These concepts are the basis for the use of an iodine tolerance test in the diagnosis of hyper- and hypothyroidism. The radioactive iodine tracer test is but one of many iodine tolerance tests that have been proposed. As far back as 1934 stable iodine was used in a test of this type, however, the chemical methods for the determination of iodine were complicated and time consuming and could not be applied routinely in clinical practice. The radioiodine tracer technique is simple and much more accurate than the older chemical methods in differentiating the various functional states of the thyroid gland.

Regardless of the exact method employed, the basic principle in the use of radioactive iodine in diagnosis is the same. A tracer dose of radioiodine is administered, usually orally, and after a variable period of time the amount of radioiodine collected by the thyroid gland, the quantity in the various blood fractions, or the amount excreted in the urine

is determined by means of a Geiger-Muller counter. The thyroid radioactivity is measured directly over the gland at a distance of 25 to 40 cm. The urine and the tracer dose are usually placed in a cup, and radioactivity measurements made at the same distance. In most laboratories the radioactivity measurements are done 24 hours after administration of the tracer dose when a relative equilibrium has been reached. Results are expressed in terms of per cent of the tracer dose administered, avoiding the difficulty and error involved in determining exact radiation units. The size of the tracer dose varies with the sensitivity of the radiation measuring instruments used. The usual dose is 40 to 100 microcuries of I^{131}. This quantity of radiation is felt to be harmless to the patient, and has no apparent effect on the function of the thyroid gland. (By use of a scintillation counter the tracer dose may be reduced to 10 microcuries or less.) The radioiodine is given without added stable iodide carrier. In this way a very small amount of iodine is administered (1 millicurie equals only .008 micrograms stable iodine), and no iodine effect on the gland occurs. Hamilton,[26] who was one of the first to use this technique, originally added 14 mg. of stable iodine carrier to the tracer dose and found poor differentiation between normal and hyperactive glands. This undoubtedly was due to saturation of the thyroid gland by the large amount of stable carrier iodine administered. The normal thyroid handles about 100 micrograms of iodine efficiently, and with larger amounts a lower and lower percentage of the administered iodine is taken up by the thyroid gland.[27] Tracer studies may be repeated in the same patient, however, it is advisable to avoid exceeding a total dosage of 200 microcuries of I^{131} in any one year.[28]

McConahey[12] found that I^{131} appeared in the blood within a few minutes after oral administration. The total blood I^{131} reached a maximum within ½ hour in hyperthyroid patients as compared to ½ to 1 hour in euthyroid and 1 to 1½ hours in hypothyroid patients. After reaching a maximum, the curve of total blood I^{131} fell more rapidly in hyperthyroid subjects. The protein bound fraction of the blood I^{131} rose more rapidly and to higher levels in the hyperthyroid patients, reflecting the increased rate of thyroid hormone production. Luellen and coworkers[29] analyzed the curves of thyroid uptake, urine excretion, and blood levels of I^{131}, and found no significant difference in the rate of accumulation of I^{131}. The "rate constant" gave good separation between normal, hyperthyroid, and hypothyroid patients with any of the three methods of measurement. A good correlation was found between the blood level of I^{131} and radioactivity measurements taken over the thigh. Clark and associates[30,31] determined the per cent of the total blood I^{131} that was protein bound 24 hours after administration of a tracer dose, and termed this the "conversion ratio." It is an indirect measure of the rate of hormone synthesis and release by the thyroid gland, and separates hyperthyroidism from euthyroidism, but gives poor separation of euthyroid from hypothyroid patients. The separation of groups with the conversion ratio was less complete than with chemical determination of the protein bound iodine.[32] The blood iodine determination, although much simpler with radioactive tracer techniques, is still complicated and impractical for routine use, and in general gives no more information than the thyroid uptake measurements.

Keating[33] studied the urinary excretion of I^{131} by plotting cumulative urinary excretion against time, and obtained an exponential curve from which four quantities were estimated; a *renal fraction* (that part of the I^{131} dose primarily excreted in the urine), a *disappearance rate* (representing the proportional rate of disappearance of I^{131} from the blood, a *renal excretion rate* (the proportional rate of excretion into the urine), and a *collection rate* (the proportional rate of disappearance into other sites than the kidney, of which the most important is the thyroid gland). There was good separation of the various thyroid functional states with the collection rate. Keating[34] also has determined a thyroidal iodide clearance, which is defined as the volume of plasma cleared of iodide per minute. He considers this to be the most exact means of determining the thyroid functional state, however, it requires simultaneous measurement of thyroid I^{131} uptake and plasma I^{131} and serial determinations.

Skanse[27] made very comprehensive observations of the basal metabolic rate, protein bound iodine in the plasma, and urinary excretion of radioactive iodine. In a control group of normal patients the urinary excretion of a 100 microcurie dose of I^{131} was 39.8 to 81.3 per cent in the first 24 hours, 0 to 11.6 per cent in the second 24 hours, and a total excretion of 44 to 87.8 per cent in 48 hours. The mean urinary excretion of I^{131} in the first 24 hours was 65.9 per cent. The control group was made up of 110 euthyroid patients. In 94 obviously hyperthyroid patients the mean 48 hour urinary excretion of I^{131} was 17.4 per cent, with a range of 1.9 to 38.6 per cent. The size of the thyroid gland had no apparent effect on the urinary excretion values, and large non-toxic goiters still gave values in the normal range. In myxedema there was considerable overlap of the 48 hour total urinary excretion of I^{131} with the normal, however, the excretion of radioactive iodine during the 24 to 48 hour period was above normal in all 26 patients studied. The mean 24 to 48 hours excretion was 22.6 per cent with a range of 15.2 to 34.6 per cent. Skanse considered an elevated 24 to 48 hour urinary excretion of I^{131} to be diagnostic of hypothyroidism if renal insufficiency, congestive heart failure, and thyroid or iodine medication could be ruled out. In 81 patients who presented diagnostic problems but ultimately were shown to have definite hyperthyroidism, the urinary excretion of radioactive iodine was in the thyrotoxic range in 93 per cent, while the basal metabolic rate was diagnostic in only 51 per cent and the

plasma protein bound iodine (chemical determination) in 86 per cent. In the entire group of patients with endogenous thyrotoxicosis (175 cases) the urinary excretion of I^{131} was diagnostic in 98 per cent, compared to 78 per cent for the basal metabolic rate and 93 per cent for the protein bound iodine level. In no case of hyperthyroidism were both the protein bound iodine and the urinary I^{131} excretion normal. The serum cholesterol was of no value in the diagnosis of thyrotoxicosis and of very limited value in the diagnosis of hypothyroidism in this study. In 84 patients with diseases simulating hyperthyroidism (anxiety neurosis, leukemia, cardiac disease, etc.) only 1 urinary I^{131} excretion value was in the hyperthyroid range, and this was in a patient with renal insufficiency. The 24 hour excretion of I^{131} was considered as reliable as the 48 hour study in the diagnosis of hyperthyroidism.

Werner and Associates[28] reported their experience with the measurement of the thyroid uptake of I^{131} in 1400 cases. A single 24 hour thyroid radioactivity measurement was made, and the urinary excretion of I^{131} was not measured. In 1000 euthyroid patients the mean thyroid uptake of I^{131} was 24.4 per cent with a range of 3 to 55 per cent. Approximately 90 per cent of the normal subjects had uptakes between 10 and 40 per cent, 2 per cent had less than 10 per cent uptake, and 9 per cent had uptakes of more than 40 per cent. In 300 hyperthyroid patients the mean thyroid uptake was 51 per cent with a variation of 23 to 73 per cent. About 11 per cent of this group had thyroid uptakes below 40 per cent. Few euthyroid patients had thyroid uptakes above 50 per cent, and very few hyperthyroid patients had uptakes below 30 per cent, and only 3 per cent of the entire group had both an erroneous thyroid uptake and basal metabolic rate. These authors feel that if the thyroid uptake and the basal metabolic rate are used together the diagnosis of hyperthyroidism will be missed in not more than 6 per cent of cases. Keating et al.[35] reported the results of I^{131} tracer studies at the Mayo Clinic in 546 patients. Of 123 thyrotoxic patients only 4 per cent had urine I^{131} excretion studies in the normal range, and in 61 cases with both thyroid uptake and urine excretion studies 5 per cent had one or the other measurement in the normal range. Kriss[36] has administered I^{131} intravenously, and in a small group of patients was able to separate hyperthyroid from euthyroid subjects with measurement of the thyroid uptake 1 hour after administration of the tracer dose. Miller has measured the thyroid uptake 2 and 3 hours after an oral tracer dose of I^{131} with as good results as when the 24 hour thyroid uptake was determined.[28] Stanley and Astwood[37] have determined a "thyroid accumulation gradient," which is derived by plotting the increase in thyroid radioactivity against the square root of time and calculating the slope of the resultant straight line. In 60 normal subjects the accumulation gradient varied from 1.4 to 36.4 with a mean of 9.4.[37]

At the present time the thyroidal iodide clearance, described by Keating[34] and Pochin and Myant,[38] is the most exact method available for the diagnosis of hyperthyroidism and hypothyroidism. However, this method requires serial and simultaneous measurements of the thyroid and plasma radioactivity, which is probably too time consuming for routine use. The determination of the 24 hour thyroid uptake of I^{131} is simple and will make the diagnosis of hyperthyroidism in more than 90 per cent of cases. When used in conjunction with the basal metabolic rate it will seldom mislead the clinician. None of the other methods described above, except the thyroidal iodide clearance, offer any real advantages over the 24 hour thyroid I^{131} uptake, and most of them are much more complicated. The urinary excretion of I^{131} is simple and as sensitive as the thyroid uptake, however, it introduces possible errors due to faulty urine collection and the presence of renal disease. The normal range for the thyroid uptake is not rigidly defined. Above 50 per cent thyroid uptake of I^{131} in 24 hours is almost diagnostic of hyperthyroidism, and below 10 per cent is indicative of hypothyroidism. Between 40 and 50 per cent thyroid uptake is a borderline zone. As in other fields of medical diagnosis, clinical judgment and evaluation of the patient will be the major factor in arriving at the final correct diagnosis.

The effect of various disease states on the thyroid uptake of radioactive iodine has been studied by several investigators.[24,27,35,39,40,41] In nontoxic goiter, nonfunctioning thyroid carcinoma, and malignant exophthalmos without thyrotoxicosis the thyroid uptake was invariably normal. In Addison's disease and acromegaly, although frequently associated with a very low basal metabolic rate, the thyroid uptake is in the normal range. Acute diffuse thyroiditis is associated with a very low thyroid uptake of I^{131} during the acute phase of the disease, becoming normal during convalescence unless myxedema occurs. In chronic thyroiditis (Hashimoto's or Riedel's struma) the thyroid uptake is usually normal even in patients with clinical myxedema.[40] Panhypopituitarism with secondary myxedema results in a low thyroid uptake, and the response of the thyroid uptake to thyrotropic hormone administration has been used in differentiating primary from secondary myxedema.[28,42] If thyrotropic hormone is administered to a patient with primary myxedema there is no effect on the thyroid uptake, however, if the hypothyroidism is secondary to pituitary insufficiency the uptake of I^{131} by the thyroid gland is increased to normal or hyperthyroid levels. Renal insufficiency and severe congestive heart failure will cause a marked decrease in the urinary excretion of I^{131}, but will not effect the thyroid uptake of radioactive iodine. Anorexia nervosa, psychoneurosis, simple obesity, hypometabolism without hypothyroidism, chronic alcoholism, essential hypertension, heart disease without decompensation, Cushing's disease, nontropical sprue, pituitary tumors without myxedema,

and various carcinomas have been studied and found to have I^{131} studies in the normal range. It is apparent that unless there is a destruction of thyroid tissue or a secondary stimulation or depression of the thyroid gland, the thyroid uptake of I^{131} is not disturbed by extrathyroid disease.

A great many factors may influence the results of I^{131} tracer studies and must be taken into consideration in the interpretation of the results. Perlmutter and Riggs[19] found that there was a gradual drop in the thyroid accumulation gradient for I^{131} in the male from puberty to senescence, and in the female there was a sharp decline after the menopause; however, the values usually did not fall below normal. There appeared to be no sex difference in the accumulation gradient at puberty, but after puberty the gradient was consistently higher in the female. These authors felt that a mechanism was present in which peripheral tissues may regulate thyroid function to some extent, and that the sex hormones might have an influence upon peripheral tissue utilization of thyroid hormone. The effect of various medications and compounds on the thyroid uptake of radioactive iodine has been reported by Skanse,[27] Werner,[28] and Keating.[35] Stable iodine ingestion will invariably produce a marked depression of the thyroid uptake due to an increase in the plasma iodine level and saturation of the thyroid gland with iodine. Iodinated compounds used in pyelograms, cholecystograms, and bronchograms all reduce the thyroid uptake of I^{131} to very low levels. Following a cholecystogram the blood iodine level may remain elevated and the thyroid uptake depressed for several months to a year, and after a bronchogram the same effects may persist up to a year or longer. This prolonged effect of gallbladder and bronchography contrast material is due to the very slow excretion of these compounds. The effect of contrast media used in pyelograms lasts for only a few days because of rapid excretion by the kidney. Lugol's solution, iodine containing cough mixtures, and tincture of iodine alter the I^{131} studies for only 1 to 2 weeks, and long term administration of these medications does not seem to prolong their effect on the thyroid uptake. Iodized table salt taken in reasonable amounts does not seem to alter the tracer studies. In general, radioactive iodine tracer studies probably cannot be reliably interpreted for 7 to 14 days after a pyelogram or inorganic iodide ingestion, 3 months after a cholecystogram, and a year or more after a bronchogram. Thyroid extract ingestion depresses the thyroid uptake for about 30 days after it is discontinued, and long term administration does not prolong its effect. Excessive ingestion of thyroid extract results in a reduction of the thyroid uptake of I^{131} to almost zero and an elevation of the basal metabolic rate and plasma protein bound iodine to hyperthyroid levels. This is the characteristic triad in thyrotoxicosis factitia. Antithyroid drugs (thioureas, thiocyanate, and food goitrogens) markedly depress the thyroid uptake of radioactive iodine, usually for only a few days. Propylthiouracil, in relatively short courses, will not alter the thyroid uptake for more than 6 days after it is discontinued.[43] A prolonged period of iodine starvation may produce an elevated thyroid uptake due to depletion of thyroid iodine stores.[28] Cortisone and ACTH may depress the thyroid uptake of I^{131} for short periods of time.[24,25] In rats, testosterone, progesterone, and estrone increased the thyroid uptake of radioactive iodine, and pregnenolone and epinephrine seemed to depress the thyroid uptake.[25]

THE USE OF RADIOIODINE IN THE TREATMENT OF HYPERTHYROIDISM

Hertz and Roberts,[3] in 1941, first used radioactive iodine in the treatment of hyperthyroidism. They treated 29 patients with a mixture of I^{130} (90 per cent) and I^{131} (10 per cent), and observed remission of the disease in 20 of the cases. The total dosage used varied from 5 to 28 millicuries. Since this first published report many hundreds more patients have been treated with radioactive iodine.

The results of I^{131} treatment in 1008 cases of hyperthyroidism, as reported by eight investigators, are summarized in table II. The patients have been divided into two groups; those with diffuse toxic goiter, and those with toxic nodular goiter. In the group with diffuse toxic goiter 96 per cent of 875 cases became euthyroid on one or more doses of I^{131}. Only 55 per cent of these patients had a remission of their disease following the initial dose of radioactive iodine. Those who did not become euthyroid after the first dose of I^{131} usually had a remission following a second dose, however, occasional patients required three to seven doses of I^{131} before remission occurred. In patients where multiple doses of radioactive iodine were necessary, with each dose of I^{131} the degree of thyrotoxicity was decreased until a complete remission was produced. If treatment had been adequate, a remission occurred within four months after the administration of radioactive iodine. The total dosage of I^{131} necessary to produce a remission varied from 0.5 to 41 millicuries, the very small doses being used mainly in patients with recurrent hyperthyroidism after thyroidectomy. The incidence of hypothyroidism following radioactive iodine therapy was found to be 7 per cent in the group with diffuse toxic goiter. If Moe's series,[49] in which the incidence of hypothyroidism seemed excessively high, is excluded, the over-all incidence of hypothyroidism is reduced to 5 per cent. The hypothyroidism produced was usually mild and easily controlled with thyroid extract. Transient hypothyroidism, occurring in the first 2 to 3 months after treatment and disappearing by 4 to 6 months after therapy, was observed in occasional patients.[47,48,51,53] Williams[48] feels that transient hypothyroidism is more common following I^{131} therapy than after surgery, probably due to temporary injury of thyroid cells by radiation with ultimate recovery.

TABLE II

RESULTS OF I^{131} TREATMENT IN HYPERTHYROIDISM

Toxic Diffuse Goiter

Author, Ref. No., Year	Number of cases	Percent in remission	Percent in remission on one dose	Time for remission aver., months	Total dose range, mc.	Aver. total dose, mc.	Percent hypothyroid
Chapman[44] 1948	65	80	74	2	4 to 14	10	6
Werner[45] 1949	103	92	61	2 to 3	3 to 6.5	—	4
Soley[46] 1949	46	96	—	under 4	3 to 10.5	—	4
Prinzmetal[47] 1949	26	96	—	3 to 4	0.5 to 10	4.4	4
Williams[48] 1949	75	100	47	3.3	—	8.5	4
Moe[49] 1950	67	100	52	3	1.1 to 17.8	5.6	15
Feitelberg[50] 1950	290	99	46	2	1.7 to 38	—	6
McCullagh[51] 1951	203	98	65	4	4 to 41	12.8	9
Totals	875	96	55			8.3	7
Toxic Nodular Goiter							
Williams[48]	22	91	—	—	14 to 36	14	0
Moe[49]	33	100	29	4.7	2.2 to 43.9	—	6
McCullagh[51]	78	77	—	5	7 to 104	—	0
Totals	133	85	29				1.5

The manner of determining an adequate dose of I^{131} to produce a remission but not hypothyroidism varies considerably among investigators directing treatment. Haines,[52] who reported the results in 40 patients treated at the Mayo Clinic, estimates the thyroid gland weight in grams and administers 200 to 250 microcuries per gram of thyroid tissue, taking into account the thyroid uptake of I^{131} as determined previously with a tracer study. The total dosage used varied from 2.6 to 20 millicuries, and a remission occurred in 27 patients after a single dose and in eight patients after a second or third dose. Hypothyroidism was produced in eight of the 40 patients. Soley[46] used relatively small dosage, administering 250 microcuries at weekly intervals up to 1 to 4 millicuries in a single dose. Werner[45] attempts to administer 5000 R.E.P. or 100 to 200 microcuries per gram of thyroid tissue, as calculated from the formula

$$\text{R.E.P.} = \frac{\mu c \times .UT}{GW} \times \frac{E.H.L.}{8} \times 160$$

wherein μc is the number of microcuries to be administered, UT is the per cent thyroid uptake of I^{131} as determined by a tracer dose, GW is the estimated thyroid weight in grams, E.H.L. is the effective half life of the administered I^{131} in days, and 160 is the number of equivalent roentgens produced by 1 microcurie of I^{131} in 1 gram of tissue if remaining for total decay. The effective half life is defined as the time in days necessary for 50 per cent of the I^{131} in the thyroid gland to be lost by both secretion and physical decay, and usually is four to seven days whereas the half life of I^{131} due to physical decay alone is eight days. The E.H.L. must be determined individually in each patient. Burrows and Ross[53] use a similar formula and feel that 7000 to 10,000 R.E.P. must be delivered to the gland to get a remission of the disease. They have found the E.H.L. to be 1.7 to seven days. Other investigators base the size of the dose to be administered just on the estimated weight of the thyroid gland, and attempt to administer to the gland a certain number of microcuries per gram of thyroid tissue. Even here a great deal of controversy exists, and in the literature as little as 23 and as much as 575 microcuries per gram of thyroid tissue has been advocated.[51] McCullagh[51] recommends a dosage schedule based on the estimated thyroid weight. He gives 4 millicuries to a 30 gram thyroid, and increases the dose by 1 millicurie for each additional 10 grams of thyroid weight. Despite the diversity of opinion and the variety of methods advocated, all methods used appear to be based on certain fundamental concepts, and most investigators seem to be getting good results with their own system of dosage estimation. It has been well established that the size of the I^{131} dose necessary to produce a remission of hyperthyroidism is directly related to the size of the thyroid gland and not to the degree of toxicity or the height of the basal metabolic rate.[48,50,51,53] The per cent thyroid uptake of I^{131} is also an important factor since the dose based on thyroid weight is that which must actually be delivered to the thyroid gland, and thus this dose must be corrected to include the radioactive iodine which, although administered, will not be taken up by the gland. The effective half life of the I^{131} taken up by the gland is important, and together with errors in estimating the thyroid weight, probably accounts for the rather poor remission rate on the initial dose of I^{131} when it is not taken into consideration. Calculation of the dose of I^{131} using

the formula advocated by either Werner[45] or Ross,[53] and attempting to administer between 5000 and 10,000 R.E.P. to the gland appears to be the soundest method for determining the dose of radioactive iodine at the present time.

Associated with remission of hyperthyroidism following I^{131} therapy, in almost all patients the thyroid gland decreases in size until it is no longer palpable. During this period of decrease in size the diffusely enlarged gland becomes firm and indurated and may at times feel nodular. Nodular glands decrease in size following radioactive iodine treatment, however, in most cases they are still palpable despite a complete remission of the hyperthyroidism. Subjective improvement of the hyperthyroidism usually begins two to three weeks after administration of the I^{131}, and objective signs of improvement are usually evident at four to six weeks becoming maximum at three to four months after therapy. Reduction in the thyroid uptake of I^{131} to normal levels may lag slightly behind the clinical improvement and the lowering of the basal metabolic rate, however, when a complete remission has occurred, the thyroid uptake of I^{131} usually is back to normal values. Recurrence of hyperthyroidism after adequate radioactive iodine therapy has been very uncommon, and is less frequent than following surgery or antithyroid drug therapy. During the first three to six months after treatment a brief transient complete remission followed by a recurrence of thyrotoxicity may occur, but even this is not common. If a remission of the disease has not occurred within four months after administration of the radioactive iodine, further treatment with I^{131} should be undertaken, the dosage calculated as before. With adequate dosage, there appears to be no reason why all patients with diffuse toxic goiter cannot be made euthyroid with radioactive iodine.

Several authors[44,46,48,49,50,53] have reported an increase in thyrotoxicity occurring in a few patients the first seven to ten days following I^{131} therapy. In some of these patients, associated with the exacerbation of hyperthyroidism, there was a rise in the plasma protein bound iodine level.[44,46] This increase in toxicity is thought to be due to a rapid breakdown of thyroid tissue following I^{131} administration and a rapid release of large quantities of thyroid hormone.[44] The use of propylthiouracil in short courses prior to radioactive iodine therapy has been recommended by some authors[44,48,51,54] in an attempt to deplete the thyroid gland of hormone, however, in most clinics no pretreatment is given except to an occasional very severely toxic patient. Following treatment with I^{131} in severely thyrotoxic patients, most investigators recommend giving propylthiouracil for two to four weeks or Lugol's solution for five to seven days to control the hyperthyroidism until an I^{131} effect occurs.[44,48,50,51,54]. Minor toxic reactions such as transient sore throat and cough, tenderness of the thyroid gland, mild radiation sickness, fever, and elevation of the sedimentation rate, occurring during the first ten days after I^{131} therapy, have been observed by a few authors, but are uncommon.[44,46,50,53] Several investigators have inadvertently administered therapeutic doses of I^{131} to women in the first and second trimester of pregnancy with no apparent ill effect on the mother or the fetus.[44,48,55] Progression or increase in exophthalmos following I^{131} therapy has been very uncommon, and in many cases improvement has been observed.[46,49,50,51] Soley[46] reported that in his experience increase in exophthalmos occurs less frequently after I^{131} treatment than following surgery, but more frequently than after deep x-ray therapy of hyperthyroidism. It seems unlikely that progression in exophthalmos is directly related to the type of therapy used for the hyperthyroidism, but rather to the frequency in which hypothyroidism is produced.

There is still some controversy concerning the selection of patients for treatment with radioactive iodine. Originally only poor surgical risks, recurrent hyperthyroidism, elderly patients, and patients who refused surgery were treated with radioactive iodine. This conservatism was based mainly on the fear of producing late carcinoma. More recently these limitations have been liberalized, and in many clinics all patients with diffuse toxic goiters are being treated with I^{131}.[47,50,51]

A few investigators have treated patients with multinodular toxic goiters, and their results are shown in table II. The remission rate is somewhat lower than in the group with diffusely hyperplastic glands, and usually multiple doses and two to three times the total dosage of I^{131} must be used in nodular glands.[48,49,51] In most cases the thyroid gland becomes smaller after treatment, however, it usually remains palpable. In general, in toxic nodular goiter a much larger total dosage of I^{131} is required for remission, fewer patients are controlled with a single dose, and a longer period of time is necessary for remission.[51] The relationship between the size of the goiter and the amount of I^{131} necessary for remission is much less clear-cut in nodular glands as compared to diffuse goiter.[51] The greatest deterrent to the treatment of toxic nodular glands with I^{131} rather than surgery is the danger of not eradicating a coexisting thyroid carcinoma, particularly with solitary adenomas.

Radioactive iodine in the treatment of hyperthyroidism has several advantages over surgical thyroidectomy. The results with I^{131} are as good or better than with thyroidectomy, the only complication is hypothyroidism, which is no more frequent than after thyroidectomy, and the expense and morbidity for the patient is much less. In most clinics the patients are not even hospitalized but are treated as out-patients. The only hazard suggested is that radioactive iodine may be carcinogenic, however, to date in cases followed as long as ten years no carcinomas have developed, and the experience with deep

x-ray therapy of hyperthyroidism would indicate that these fears are unfounded.

THE USE OF RADIOIODINE IN THE TREATMENT OF THYROID CARCINOMA

The basis and the fundamental requirement for the use of radioactive iodine in the treatment of thyroid carcinoma is that the tumor tissue take up iodine. Deep x-ray therapy can be given to the thyroid region only up to a maximum of 6000 to 9000 roentgens, mainly because of the damage to the skin and normal vital tissues in the neck. This also holds true for the treatment of metastases. Radioactive iodine can be given in quantities resulting in 40,000 equivalent roentgens, four to six times the amount of radiation that can be safely administered with deep x-ray.

The great limitation in the use of radioactive iodine in thyroid carcinoma is the poor iodine uptake of most thyroid carcinoma tissue. It has been demonstrated by several investigators that the iodine uptake of thyroid carcinoma tissue is almost directly related to the amount of follicular tissue and colloid present in the tumor. Fitzgerald and Foote[56] studied the I^{131} uptake of 100 specimens of thyroid carcinoma obtained at operation, biopsy, and autopsy. Seventy-four per cent of 39 follicular and alveolar carcinomas took up appreciable amounts of radioactive iodine; the concentration of I^{131} usually varying directly as the ratio of colloid to the total amount of tumor tissue present. Occasional tissues with alveoli but no colloid took up radioactive iodine, and some tissues with follicles and colloid did not take up I^{131}. Pure papillary carcinoma, solid carcinoma, Hurthle cell carcinoma, and undifferentiated carcinoma did not take up significant amounts of I^{131}. In none of the tissues did the carcinoma take up as much I^{131} as did the adjacent normal thyroid tissue. Similar results have been reported by other authors.[57,58,59]

Several methods have been employed to induce radioactive iodine uptake in metastatic thyroid carcinoma tissue. Trunnell[60] reported studies in 25 patients with thyroid carcinoma and metastases, and in only one patient did the metastases take up enough I^{131}, before removal of all normal functioning thyroid tissue, to make treatment possible. After total thyroidectomy, either surgical or with radioactive iodine, it was found that one or more metastases in 12 of 23 patients concentrated considerably more I^{131} than previously. In three of six totally thyroidectomized patients, treatment with thyrotropic hormone caused further increase in the I^{131} uptake by the metastatic tumor tissue. Ten patients, in whom metastases had shown increased I^{131} uptake after total thyroidectomy, were treated for several months with thiouracil or propylthiouracil, and in seven of the ten patients a further increase in I^{131} uptake was observed. Seidlin[57] found that in the presence of normal thyroid tissue, metastatic carcinoma lesions had low or no I^{131} uptake. By total thyroidectomy or thyrotropic hormone stimulation he was able to induce radioactive iodine uptake in many cases. It has been observed that occasionally as one metastatic lesion is destroyed by radioactive iodine, another begins collecting I^{131} and can be treated. Rall and co-workers[61] reported that with a combination of total thyroidectomy and prolonged thiouracil treatment they were able to induce collection of I^{131} in 21 of 35 metastatic thyroid carcinoma lesions, and as a result were able to treat 16 of these patients with radioactive iodine.

The results of treatment of metastatic thyroid carcinoma with radioactive iodine have been encouraging, although most of the patients treated have had advanced disease and widespread metastases. Seidlin[57] treated 12 patients with I^{131} over a six year period. Seven are alive, and of these 3 are greatly improved, 2 are moderately improved, and 2 are stationary. Three of the 5 patients who died showed sustained improvement following I^{131} therapy, and it was felt that their lives had been prolonged. Marinelli[58] reports radioactive iodine treatment of a patient with alveolar adenocarcinoma of the thyroid who had widespread metastasis and was moribund. He responded remarkedly to I^{131} treatment, gained 55 pounds in weight, and was able to return to normal activities, although he still had viable tumor tissue. Trunnell[60] treated 9 of 25 functioning metastatic thyroid carcinomas with I^{131}, and 4 of the 9 patients showed definite improvement as evidenced by decrease in tumor mass or by distinct histologic evidence of tumor destruction. Freedberg[62] reported the treatment with I^{131} of a 14 year old boy with thyroid papillary carcinoma, metastatic to the lung following total thyroidectomy. The pulmonary lesion disappeared and the patient became myxedematous after radioactive iodine therapy. Clark[63] has reported disappearance or improvement of metastatic lesions in 8 of 15 patients treated with I^{131}. Similar results have been reported by Rawson[64] and Horn.[65]

The dosage of radioactive iodine in the treatment of thyroid carcinoma has varied a great deal. Most investigators use single doses in the range of 50 to 100 millicuries, however, as much as 200 millicuries has been administered in a single dose without serious ill effect. Total dosage of 500 to 1000 millicuries has been given over a period of several months. Toxic effects from these large doses of I^{131} have occurred. Trunnell[60] observed appearance of severe transient thyrotoxicosis following treatment, apparently due to breakdown of thyroid tissue with the release of large amounts of thyroid hormone. This may be averted by pretreatment with propylthiouracil or thiouracil. He also observed the appearance of menopause in women who were treated with large doses of I^{131}. Depression of the peripheral blood elements and the bone marrow also has been observed. One patient died of pancytopenia following treatment. Local heat and pain over the

thyroid gland and severe radiation sickness has occurred after large doses of radioactive iodine.

At the present time it would appear that thyroid carcinoma is best treated as follows: 1. Total thyroidectomy and excision of local metastasis should be accomplished surgically as the first step in treatment; 2. This should probably be followed by large doses of deep x-ray to the neck; 3. Metastases to distant sites should be treated with radioactive iodine if possible, using thyrotropic hormone and one of the thiourea derivatives in an attempt to induce the uptake of iodine; 4. Radioactive iodine tracer studies should be done at frequent intervals searching for new functioning metastases.

SUMMARY

1. Radioactive iodine tracer studies are a simple means of studying thyroid physiology, and a reliable method for the diagnosis of hyperthyroidism and hypothyroidism.

2. Radioactive iodine appears to be effective and safe for use in the treatment of most hyperthyroid patients.

3. Radioactive iodine should be used in conjunction with surgery in the treatment of thyroid carcinoma, if iodine uptake is present or can be induced in the carcinoma tissue.

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Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation

A Clinical Study

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STUDIES of the efficacy and methods of action of various bulk laxatives have been reported by many authors,[1–4] and have aroused an interest in other forms of mild laxatives – in this instance, malt soup extract. Although there is considerable supporting literature relative to the laxative effect of malt soup extract in pediatrics,[5–9] the application to geriatrics is comparatively new. We have recently, by clinical methods alone, studied the response of the geriatrics patient to malt soup extract from the point of view of laxative action.

Studies were carried out at Long Island Hospital, a chronic disease hospital at Boston, Massachusetts, on 24 permanently institutionalized, semi-ambulatory, severely constipated patients. In order to rule out dietary and incidental factors, 10 non-constipated patients of the same age groups were followed as controls. Subjects under study were selected from a large group of constipated patients among the 1,400 institutionalized patients in this hospital.

The preparation under study, a malt soup extract,* consists of a water-soluble mixture of sugars and grain extractives processed from barley malt. This substance has been widely manufactured and used; it differs from malt extract in that the final mixture, normally acid, has been neutralized with 1.1 per cent potassium carbonate. The resulting extract is high in maltose (58 per cent) and dextrins (12 per cent). It contains 0.9 per cent potassium, 0.1 per cent sodium, and traces of iron, magnesium, and phosphorus. The balance is made up of water-soluble grain extractives and moisture. The finished product, a dark brown, thick liquid, has a mildly sweet taste and is readily soluble in water. Barley malt has a high B vitamin content, but this is largely destroyed in manufacturing malt soup extract. The presence of other accessory growth substances as discussed by Astrup and others in Copenhagen[10] is beyond the scope of this paper, which deals only with the laxative effect.

The efficiency of this substance in softening stools is extensively discussed in pediatric literature.[5–8,11,12] This action is dependent upon the proportion of readily fermentable maltose, which encourages the growth of aciduric bacteria and retards the growth of putrefactive bacteria.[5,13,14,15] An excess of maltose tends to reach the lower intestine and contributes further laxative action.[8] The water-soluble barley grain extractives further the action.[6] The exact contribution of potassium in the process is difficult to determine but it is known to be helpful.[6,8,16]

Diabetics were excluded from the study because the medication has a high carbohydrate content.

Observations were made daily on all patients for 5 weeks, and included number of bowel movements, consistency of the stool, and presence or absence of side effects, such as gas, cramps, nausea, diarrhea, throughout the entire period of laxative administration. Convenience of administration and patient acceptance were also considered. Control observations were made for two weeks before starting the medication.

The general scheme of this test is given in table I. It will be noted that groups 1 and 2 received dry malt soup extract, a dessicated form of the extract, and groups 3 and 4 the liquid

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*All medication provided by Borcherdt Malt Extract Company, Chicago, Illinois.

TABLE I

DAILY DOSAGES IN TABLESPOONFULS FOR ALL GROUPS

	No. of patients	*Medication*	CONTROL PERIOD		TEST PERIOD				
			First week	*Second week*	*Third week*	*Fourth week*	*Fifth week*	*Sixth week*	*Seventh week*
Group 1	6	Dry malt soup extract	0	0	4	2	4	4	4
Group 2	6	Dry malt soup extract	0	0	2	2	4	4	4
Group 3	6	Malt soup extract	0	0	4	2	4	4	4
Group 4	6	Malt soup extract	0	0	2	2	4	4	4
Group 5 (Control)	10		0	0	0	0	0	0	0

Dry malt soup extract: 1 heaping tablespoonful = 19.7 grams (18.9 grams of solids).
Malt soup extract: 1 tablespoonful = 28.0 grams (21.9 grams of solids).

form. The difference in clinical response between groups 1 and 2 and groups 3 and 4 is small. We intended originally to determine whether high doses over a relatively short period were more or less effective in softening the stools than smaller doses over a longer period, but it did not prove practical to carry out this investigation. In the groups receiving the lower dosage, and in the other groups when dosage was reduced for comparison, patients complained about the lack of frequency of stools, and medication was promptly restored to the larger volume. The resulting data were evaluated both clinically and statistically and subjected to statistical analysis.[17]

During the control period of 14 days we found it impossible to discontinue laxation entirely for those patients accustomed to laxatives. Panic ensued on about the third or fourth day if an evacuation were not forthcoming, and an enema or the previous laxative had to be administered. During the pretest observation period of 2 weeks, laxatives had to be administered 28 times in all. This compares with only one laxative and one enema administered during the 5 week test period when patients were receiving the malt soup extract supplement daily. The control period thus served to establish the resistant and constant state of the constipation, and further highlights the results observed during the test period.

In the control group, statistical analysis showed that neither regular hospital diet or environment had any influence on the frequency of bowel movements during the 7 weeks of observation. Thus influences other than laxatives on the bowel characteristics were eliminated in our test group of 24 patients.

No differences in bowel movement frequency were shown during the control period and during the five weeks of administration of medication, neither were there any significant differences between any group or combination of groups in regard to effectiveness of the dry and the liquid malt soup extracts.

The group of constipated patients had approximately one-half as many bowel movements as the control group of non-constipated patients during both the pretest and test periods. It appears, therefore, that frequency of bowel movement was not influenced by the taking of malt soup extract and that frequency did not increase during the test period.

The state of the stool was, however, universally altered by the treatment with malt soup extract. The stools were softened and remained soft in all cases, and the movement always followed spontaneously, eventually, as is indicated by the elimination of extra laxatives. No side effects of any sort were observed.

Seven patients (29 per cent) expressed a desire to remain on the test medication in preference to previous laxation.

DISCUSSION

The laxative required in the adult may or may not be the same as that required in the infant. The bowel in a normal, healthy infant has probably an optimum of frequency expectancy. When food is introduced into the upper intestinal tract, there is a reflex stimulation of the lower tract and evacuation shortly ensues. This action is prevented only when excess absorption of water or other factors produce inspissation of the stool, and the normal contractures are consequently unable to produce emptying. In such cases, all that is needed is a material that permits the stool to remain soft. No laxative is re-

quired, but rather a bowel content modifier. In adults, the same principle, ideally, should apply. Since, however, in the older individual a gradual decrease in bowel tone may further modify the expected frequency of evacuation, it is desirable to establish a baseline of normal periodicity of bowel movements before proper evaluation of any laxative is made. Various degrees of tone may be encountered; in other words, given a normal soft stool, the bowel may be expected to empty itself every day, second day, or even up to 5 days. Superimposed on the natural periodicity are the emotional setup, the status of acquired habits, the pressure from advertising, and the personal whim. Somewhere we arrive at the individual optimum of frequency.

Malt soup extract effectively modified the consistency of the stool without side effects. The stool became soft in all cases but there was no increase in frequency of evacuation. The frequency of the constipated patients was still approximately half that of the non-constipated patients.

The reduced number of enemas required during the study period in contrast to that of the control period, showed that the medication was effective in permitting emptying at an adequate interval. The stool at enema was soft and the enema was given only because the patient did not have the bowel movement he desired.

CONCLUSION

Malt soup extract appears to be an effective bowel content modifier in older patients. It produces soft, easily evacuated stools without any side effects, but it does not have the force necessary where immediate laxation is desired.

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Profound anemia, weakness, weight loss, and alternating bouts of constipation and diarrhea are typical of carcinoma of the right colon. The chief symptom usually is pain in the right lower quadrant or the lower part of the abdomen. In 10 per cent of cases, acute appendicitis is a complication of the malignant growth; in 3 to 15 per cent, an appendectomy is performed before the carcinoma is diagnosed.

When an elderly patient is operated upon for acute appendicitis, the right colon should be examined for a possible malignant lesion in the cecum. The incision should be wide enough to permit tihs examination.

In reviewing 29 cases of acute appendicitis with carcinoma of the cecum, John F. Thomas, M.D., of Austin, Texas, states that when the cancer is not recognized and removed at the time of surgery for appendicitis, a prolonged, complicated course is initiated. Six months ordinarily pass before an accurate diagnosis is made. By this time the tumor may become inoperable.

John F. Thomas: Carcinoma of the cecum. Texas State J. Med. 49:222-226, 1953.

Andrew T. Rasmussen

Scientist, Educator and Humanitarian

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The name Rasmussen — Andrew, Theodore, and Waldemar — signifies excellence in neuroanatomy, neural surgery, and clinical neurology. Andrew Rasmussen was born from a long line of Danish blacksmiths in Spring City, Utah, August 10, 1883, and he himself worked in his father's blacksmith shop until he was 19 years old. His ancestors were located in Utah by Mormon missionaries working in Denmark.

In order to attend high school and college, it was necessary that he leave home and earn his own living. During three summer vacations, he was employed as a shepherd in the Rocky Mountains. For three more summers he worked with a crew of surveyors in the Uinta Indian Reservation and Green River, Wyoming.

In high school he did excellent work and was active in student organizations, serving as president of the senior class in 1905. The next year he taught mathematics, science, and art in a small high school in Vernal, Utah.

At Brigham Young University his interest changed from mathematics to psychology and finally to biology. For two years he was president of the student body which at that time managed nearly all extra-curricular activities such as debating and athletics. He also represented the university in intercollegiate debate in 1906 and 1907.

After receiving the degree of Bachelor of Arts in 1909, he was made assistant professor and two years later head of the Department of Biology at Brigham Young University. That year he married Gertrude Brown, daughter of Professor Brown, then dean of the School of Education. His summers were devoted to graduate studies such as bacteriology, physiology, neuroanatomy and psychology at the University of Chicago.

From 1913 to 1916, he was instructor and graduate student in the Department of Physiology at Cornell University, under the guidance of Dr. Sutherland Simpson, and was granted his Ph.D. in physiology and anatomy in 1916. Dr. Simpson and Dr. A. T. Kerr, with whom he took a minor in anatomy, considered Dr. Rasmussen the best student they had taught.

Dr. C. M. Jackson, one of America's most renowned anatomists, offered Dr. Rasmussen an instructorship in anatomy with an annual salary of $1500 at the University of Minnesota. He accepted and his work beginning in the fall of 1916 was of such high quality that he was promoted to assistant professorship in 1918, associate professorship in 1919, and professorship in 1925.

Andrew Rasmussen's acceptance of the Minnesota post was the beginning of one of the finest teaching and research programs in neuroanatomy of all time. He assembled a unique collection of demonstration material for teaching. His "Laboratory Directions in Neuroanatomy," with

42 pages of directions, is now in its third edition.

Another volume of 117 pages entitled "Outlines of Neuroanatomy" was also written by Dr. Rasmussen for his course. This contains 103 excellent illustrations and has reached the eighth printing of the third edition. He prepared a third volume of 73 pages, under the title "The Principal Nervous Pathways," which is one of the most extensively used books in neuroanatomy. Four editions of this book have been published. Of great help to the student is the "Atlas of Cross-Section Anatomy of the Brain," by Villigar, Ludwig and Rasmussen. This volume contains 65 excellent illustrations, the sagittal series being made by Rasmussen.

Dr. Rasmussen, a medical artist in his own right, has produced large numbers of drawings and illustrations for his books and scientific articles. By his demonstration and books, which are used as texts in many medical schools, he has greatly facilitated the teaching of neuroanatomy. He himself has taught this course to more than 4,000 regular medical students and about 200 postgraduates.

Dr. E. A. Boyden, director of the Department of Anatomy, says:

Faculty and students alike will miss Dr. A. T. Rasmussen after 36 years of distinguished service in the Department of Anatomy. He became known as an authority on the anatomy of the pituitary gland and as one of the leading neuroanatomists in the country. In this school he will long be remembered for his conscientious service as chief examiner and as one of the most inspiring and competent teachers in the basic sciences.

Dr. H. S. Diehl, dean of the medical sciences who has been intimately associated with Dr. Rasmussen for 36 years, says:

Throughout Dr. Rasmussen's long period of service as professor of neuroanatomy, he brought credit to himself and to the University as a distinguished scholar, an inspiring teacher, and a productive scientist. Whether Dr. Rasmussen was instructing undergradate, medical or dental students or directing the work of Ph.D. candidates, he brought to the classroom and laboratory so much enthusiasm and such deep understanding of his subject that the difficult became easy and the students carried away with them an inspiration for the subject. Such individuals on the faculty make for a great university and Minnesota is fortunate indeed to have had these many devoted and productive years of service from Dr. Rasmussen.

In addition to developing outstanding medical school courses in neuroanatomy, Dr. Rasmussen held a prominent position and was one of the most popular members of the graduate school faculty. Concerning his work in this field, Theodore Blegen, dean of the Graduate School, says:

I cannot praise too highly the constructive contributions of Dr. Andrew T. Rasmussen to graduate studies and the graduate school through his many years of service, but the truth is that they do not need praise. They speak for themselves.

I find, for example, that he himself has been the principal adviser of fifteen students who qualified for the degree of Doctor of Philosophy. They are spread over the period from 1926 to the present. Look out over the country and you will find them in very important positions. They represent the idea of The Greater University. They are extensions of the influence of Dr. Rasmussen far beyond the boundaries of our campus. You will find them as professors in Washington University, the University of Texas, the University of West Virginia, University of Maryland, the Medical School at Buffalo, the Hahnemann Medical College, University of Kansas. You will find them in the Providence Hospital of Portland, Medical Department, Motion Picture Relief Fund, Inc., Los Angeles, University Health Service of West Virginia, the Medical Center of New York, and in private medical practice. Two of them are on our own medical faculty. Everywhere they bear the marks of the high and scholarly standards of medical science that have been characteristic of Dr. Rasmussen as an embodiment of the twin ideas of original research and splendid advanced training for the research problems of the future.

The graduate school and I personally take pride in paying our meed of honor and respect to this great man of teaching and research.

Dr. Henry W. Woltman, chairman of the sections of neurology and psychiatry, Mayo Clinic, and professor of neurology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, writes:

"I'd rather step down from the chair than dribble out of it," said Thomas Huxley on contemplating his retirement from the presidency of the Royal Society. Thus, it seems to us, his students and colleagues, did Dr. Rasmussen, intellectually and physically vigorous, esteemed and beloved, leave his post as professor of anatomy at the University of Minnesota.

Among Dr. Rasmussen's warmest admirers are the graduate students of the Mayo Foundation who had the privilege of studying neuro-anatomy under him. Clinical neurology and neurosurgery especially, and certain other fields of medical practice such as ophthalmology, otology, psychiatry and psychology, owe their stability to the sciences that underlie them, and perhaps the most basic of these is neuro-anatomy. Thus it is essential that graduate students in these fields be given an opportunity to review this subject. Since we could not, until recently, give a satisfactory course in neuroanatomy in Rochester, we naturally appealed to Dr. Rasmussen. His response was instant and generous. Over a period of twenty-five years, from 1923 to 1948, some eighty graduate students, the first of whom was Dr. J. W. Kernohan, went to Minneapolis to take this "refresher" course.

From the reports it would be difficult to say who enjoyed the work more, the teacher or the students. Dr. Rasmussen's enthusiasm for the subject he taught must have been contagious for the students went to his laboratory morning, afternoon and often in the evening. Regardless of time, he invariably appeared and went to work with them. His lectures were illustrated by drawings—he is a good draftsman— and were followed

by demonstrations of the gross and microscopic structures that had been discussed; reviews of interesting historical events were interwoven; recent discoveries were reported; current errors, moot points and supposedly established facts were submitted to careful circumspection. Dr. Rasmussen's teaching, however, was not a cacophony of neuro-anatomic details, painfully remembered by his students from a course they once painfully had taken. Under Dr. Rasmussen's guidance appeared nature's great design of a nervous system in action. It became clear to each student in what manner this system concerned his particular specialty. Dr. Rasmussen's outlines and books presented the facts precisely and compactly. As one student, who might have spoken for all, expressed it, "Of all medical courses I have taken anywhere, his was the best remembered and the one most actively participated in by the students. Perhaps there are other neuro-anatomists who are as well known as Dr. Rasmussen, but as a teacher he was unsurpassed. Thanks to him, when I operate on a certain structure, I know exactly what lies beside and beyond it and what would happen were I to injure it."

Dr. Rasmussen's demonstration collection comprises some 500 specimens gathered over a period of more than thirty years. Some of these are exceptional dissections, made by graduate students, whose names are generously acknowledged in the legends. Specialized nerve endings that one reads about in books, but never sees, are to be found there. Microscopic sections were gleaned from various laboratories here and abroad. Usually these were exchanged for instructive Marchi preparations that Dr. Rasmussen had made. A specimen thus acquired was usually the best, and sometimes the only, one the investigator had. Investigators in neuro-anatomy throughout the world testify to Dr. Rasmussen's generous donation to them of neuro-anatomical specimens which he thought would be of interest to them. A few of the specimens that make up the demonstration collection were prepared by Dr. Rasmussen while he was at Cornell. The J. B. Johnston collection supplied many fine specimens. In a sense the material represents a repository. A lettered display card with drawing accompanies each specimen, giving its origin or source, the technique employed in its preparation and a statement of what it demonstrates.

Shortly after Dr. Barany had been awarded the Nobel prize, he came to this country to give a series of lectures on neuro-otology, with emphasis on the relation of centers that govern movements of the eyes to the vestibular and cerebellar mechanisms. On the invitation of Dr. Newhart, Dr. Barany went to see the demonstration Dr. Rasmussen had set up for the regular medical students. As Dr. Barany inspected the sensory areas and neural connections which represented the anatomic basis of his own observations, he volunteered the information that it was the first time he had really seen these structures. Dr. Erling Hansen related that about five years ago Dr. Allan Woods of Johns Hopkins University and Dr. Lawrence Post of Washington University visited Dr. Rasmussen's laboratory. After an hour and a half of enthusiastic study of the collection, a commitment for early afternoon required their presence. As evening approached Mrs. Post became somewhat concerned for the doctors had not returned to the hotel. Eventually they were located in the laboratory still looking at "the finest thing . . . . anywhere in the world." The collection remains at the University of Minnesota.

Our students who attended Dr. Rasmussen's course at the university have a feeling of warm, personal friendship for him and I know this is mutual. Since the students were strangers in the city, Dr. Rasmussen often called to their attention important historical places and social or theatrical events, told them how to get where they wanted to go and arranged transportation, often by providing it himself. The students also met Mrs. Rasmussen and speak of her affectionately. Students and their wives visited the Rasmussen home and they recall with laughter the place cards at the dinner table, such as one on which was drawn a cerebellar cyst from which fluid escaped through a needle. These, then, provided the texts for after-dinner talks.

Dr. Rasmussen is one of the greatest teachers of neuro-anatomy of our time. He built up probably the most outstanding collection of gross and histologic neuro-anatomic specimens in existence. By his students he is remembered, also, as a warm and generous friend who did much to shape the course of their lives. They wish him well and could not bear the thought of his not working. This will not be required of them for Dr. Rasmussen will continue to work in his new home in California.

Dr. Rasmussen was succeeded by a long time intimate friend, Dr. Olaf Larsell, who previously directed the work in neuroanatomy at the University of Oregon. He says:

Dr. Rasmussen's scientific contributions have been made in three fields, namely, endocrinology, neuro-anatomy, and organization of instruction in the latter subject. His early work, begun at Cornell University, was in physiology, with especial reference to the cause of hibernation in animals. The problem was first approached by a study of blood changes in the woodchuck, published in 1915. Further studies of the blood, cytological study of nerve cells as to variations in the Nissl substance and of mitochondria, and investigation of seasonal changes in the interstitial cells of the gonads of this animal followed. Many of these studies, begun at Cornell, were completed after he came to the University of Minnesota in 1916.

Some of the theories of hibernation pointed to the hypophysis as a factor, leading Dr. Rasmussen to begin an intensive histological study of this organ. This was continued over a period of years, resulting in valuable contributions on the numbers and proportions of the several cell types, the size and proportions of the component parts of the human male and female hypophysis, and its innervation. These investigations resulted in an impressive total of carefully established anatomical fact, published in a series of papers, some under joint authorship, in endocrinological and anatomical journals.

Dr. Rasmussen's contributions to neuro-anatomy have dealt chiefly with the more exact determination of the course and connections of various fiber tracts, as shown by the Marchi method in experimental animals and, in cooperation with Dr. W. T. Peyton, in human material that came to autopsy at the proper interval, after degeneration of nerve fibers had begun, to make this technique applicable. His investigation of the central vestibular pathways, published in 1932, is still regarded as the most complete and accurate study of this difficult subject. The studies on various human fiber tracts, with Dr. Peyton, have not only scientific value, but are of practical importance to the neuro-surgeon.

It is pleasant that we his colleagues can express in some measure our appreciation while, although retired from active academic duties, his interests and zeal are keen as ever.

Dr. Rasmussen holds membership in many of the learned societies in anatomy and closely allied fields. He has been vice-president of the Association for Study of Internal Secretions, and of the American Association of Anatomists, of which he was also a member of the executive committee.

At the seventy-eighth annual commencement of Brigham Young University on June 8, 1953, Dr. Rasmussen was presented with the distinguished service award, which is given annually to not more than five individuals selected by the alumni association of the school.

Obviously to accomplish so much one must be a prodigious worker. Dr. Rasmussen has never worked by the clock, but until the job is done. He belongs to the group of whom Longfellow wrote:

> *"The heights by great men reached and kept*
> *Were not attained by sudden flight*
> *But they while their companions slept*
> *Were toiling upward in the night."*

Over the years it has not been unusual for Dr. Rasmussen to arrive at his office and laboratory at 4 o'clock in the morning and work continuously for 15 hours or longer.

In all his work, Mrs. Rasmussen has constantly encouraged and supported him. Their four children are all university graduates. Theodore B. is chief of the department of Neuralsurgery, University of Chicago; Waldemar C. is instructor in neurology, Mayo Foundation, Rochester; Richard C. holds a position in the securities business in San Francisco; and Charlotte is the wife of Dr. W. L. Roberts, an ophthalmologist in Los Angeles.

My acquaintance with Andrew Rasmussen began in the graduate school of Cornell University in the summer of 1913, and led to a close association and valued friendship which has extended over four decades. For several years we worked together in the Department of Anatomy, University of Minnesota, under the direction of Dr. C. M. Jackson, to whom we are both deeply indebted. Our children grew up together. The Rasmussens are every ready to make personal sacrifices and put forth any amount of effort to help their friends, and their loyalty and dependability are unsurpassed. When they informed us that they were planning to move to another state following Dr. Rasmussen's retirement in June, 1952, we were shocked with the thought that our long and pleasant association was to be interrupted. However, our lives have been greatly enriched and will continue to be so by frequent contacts with the family. We watched him assemble the world's finest collection of neuroanatomic specimens. We observed his teaching of thousands of students. We have watched him as he worked on his fine research projects and as he prepared his superb manuscripts. We have seen the unexcelled kindness and helpfulness to others which, with professional achievements won for him a place among Minnesota's renowned citizens.

The Rasmussens are now living at 4636 Indianola Way, La Canada, California. Dr. Rasmussen has been offered generous laboratory and other facilities in four institutions in the Los Angeles area. There they will soon enjoy the deep affection and sincere esteem of their associates as they now do of all who have previously known them.

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Clinical Note:

Prevention of Accidental Salicylate Poisoning in Children

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Accidental poisoning from salicylates—probably the world's most widely and most indiscriminately used drugs—is comparatively rare, although salicylates are certainly not innocuous. The total number of accidental deaths from this group of drugs, however, is not negligible, as demonstrated by 526 fatalities caused by salicylates between 1933 and 1943.[1] The vast majority of poisonings and deaths occur in the age group between the first and fourth year of life.

The child entering his second year has gained the freedom of moving about without aid, and uses this faculty to become acquainted with objects in his surroundings. His insatiable curiosity, however, is not yet controlled by judgment. The dangers of that unrestricted curiosity are increased, because for him the mouth still is a means both for sensual gratification and exploration of objects.

An increase of salicylate poisoning may be on its way because of the present trend towards improving the taste appeal of pharmaceutical products.[2] Even without the lure of taste, the tablet form, as such, stimulates the child's curiosity. While it is often an ordeal for the mother to coax her child to swallow a single tablet, when the idea is self-motivated, the child finds great fun in swallowing whole handfuls of tablets until the bottle is empty.[3]

The problem of preventing these tragedies is not an easy one for the drug manufacturer to solve. When enticing taste and tablet form are ruled out, difficulties of administration increase. In the case of aspirin, however, this dilemma has been overcome by a new preparation° which presents aspirin as a powder which readily dissolves in water and other liquids without a trace of taste or visibility; hence, children accept it readily. Furthermore, since a powder does not have a particular visual or tactile attraction, this preparation does not tempt the child's curiosity.

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°Crystar, manufactured by The Armour Laboratories.

Section on PAIN

THE SECTION ON PAIN *is fortunate in having obtained articles from Doctors Warren Wilhelm and Frank Krusen and from Dr. Lucian A. Smith. Doctors Wilhelm and Krusen have had an almost unparalleled opportunity to observe the pain and distress that must be endured by those who are seeking physical rehabilitation and their remarks, therefore, on this subject are extremely worthwhile and helpful. I have known of the work that Doctor Smith and the late Dr. Andrew B. Rivers did over a period of many years on the question of pain patterns in connection with lesions of several intra-abdominal organs. The fact that a book entitled, "Peptic Ulcers: Pain Patterns, Diagnosis and Medical Treatment," which has just appeared on the market under the authorship of Doctors Smith and Rivers, will help physicians to diagnose certain diseased organs quicker and more accurately than before. An extensive book review of this book will appear in the January issue.*

I am glad to say that the January 1954 issue of the Section on Pain will contain two articles that should be of great interest, especially to those physicians in the specialty of eye, ear, nose and throat. One article by Dr. Hugo Bair is entitled, "Differential Diagnosis of Ocular Pain", and the other, "Somatic Head Pain from the Standpoint of the Rhinologist, Otologist and Laryngologist" by Dr. Henry L. Williams. Because of the limited number of copies of THE JOURNAL-LANCET *that are published to meet the ordinary needs, it is becoming more and more clear that certain issues, notably those of May and June 1953 on "Potassium Metabolism", become in great demand and yet are out of print. It is, therefore, suggested to you who read these introductory remarks that you call the attention of any one who you think might be interested in the contents of the forthcoming January issue.*

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Pain Patterns in the Diagnosis of Upper Abdominal Diseases

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TRUE VISCERAL sensation is transmitted to the conscious level by visceral afferent nerve fibers which mediate suitable stimuli from the viscera. Since viscera are insensitive to many stimuli such as cutting, burning, and crushing, impulses transmitted usually result from tension, such as that produced by distention of the lumen or by spasm of the smooth muscle of a hollow viscus. The afferent fibers pass by way of the splanchnic nerves without synapse, through the sympathetic trunk and white rami communicantes to the posterior root of the spinal nerve in which the ganglion-cell bodies are found. The ganglion cells, which are mostly of the unipolar variety, have similar fibers connecting them with the spinal cord by way of the posterior nerve root. It is probable that the clinical phenomenon of summation of pain occurs at this level in the spinal cord. In the summation phenomenon, multiple or maximal adequate stimuli exceed the individual's threshold for pain and may be felt in ordinary visceral zones and additionally in appropriate somatic zones.

Somatic pain is mediated by the segmental cerebrospinal nerves. In the abdomen these trunk nerves supply the body wall, the parietal peritoneum, the mesentery of the large and small intestines, and the lesser omentum. The greater omentum does not have cerebrospinal innerva-

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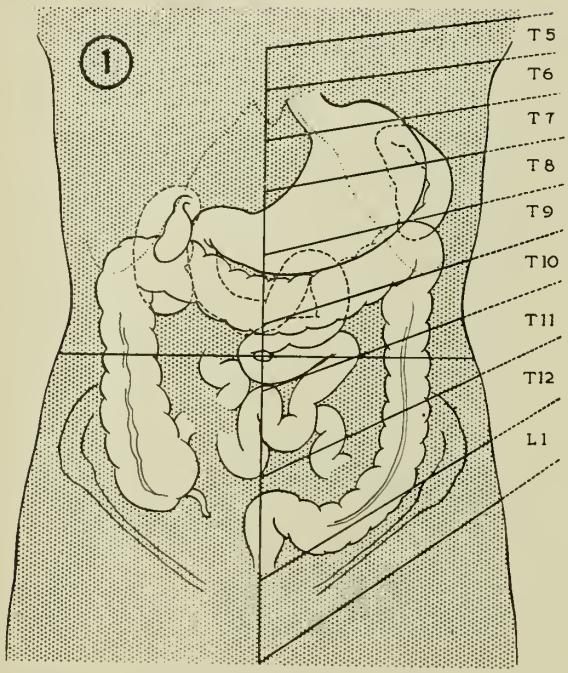


Fig. 1. Some of the important viscera of the abdomen and the dermatomes at various levels.

tion. Pain transmitted from the parietal peritoneum can be localized by the patient because of the fairly accurate sensory dermatome arrangement. A diagram of the trunk and some of the important viscera concerned in pain is shown in figure 1. The levels of the dermatomes are superimposed. It will be noted that the region about the xiphoid process of the sternum is at the level of the sixth thoracic dermatome, that the umbilicus is in the tenth thoracic dermatome, and the inguinal ligament is in the first lumbar dermatome. To a lesser degree of accuracy, the mesentery receives its innervation in accord with the origin of the viscera. For example, the lesser omentum and its structures arise in the sixth thoracic dermatome. The mesentery of the small bowel arises in the tenth thoracic dermatome. The mesocolon has its origin corresponding to the lowest thoracic dermatome. There is an overlapping in the segmental dermatomes.

Pain patterns in the abdomen are for practical purposes dependent on the amounts of visceral and of somatic fractions involved in the total pain. Naturally, variation occurs depending on the nature of the visceral lesion; that is, whether the lesion is primarily obstructing or primarily perforating. The location of the lesion determines which contiguous organs or somatic nerve pathways are involved if perforation occurs. The response of the patient to pain depends on his threshold to pain and presumably also on how well he is supplied with nerve pathways. Care should be taken to distinguish between sensitivity to pain and the outward manifestation of nervous tension.

The quality of pain produced by stimulation of the parietal peritoneum and of the mesentery (somatic pain) differs from that mediated by the splanchnic pathways. The pain which arises as a result of stimulation of the peritoneal surfaces by inflammation has a difference which is described frequently by the patient as sharp, stabbing, or knifelike. Usually such a pain is described better than is the nauseating, cramplike, visceral pain. The pain of peritoneal irritation secondary to a penetrating ulcer is often described as boring, steady, or in some instances resembling a toothache. It does not have the intermittent fluctuating quality of cramping or gnawing visceral pain. Peritoneal traction, friction, torsion, or chemical, thermal, and bacterial stimulation may cause such somatic pain. This type of pain may be aggravated by bending over, walking, running, jarring, going up or down stairs, or riding in an automobile on a rough road. Movement makes somatic pain worse but visceral (splanchnic) pain may be relieved by motion, pacing, doubling over, or by other positions.

Localization of a lesion from the consideration of its pain pattern may be difficult. In general, splanchnic pain is a midline abdominal pain and is of little value in lateralizing the lesion. For example, pain in the infraxiphoid region or high in the epigastric region may be associated with nonperforating lesions of the gallbladder or bile ducts, the stomach or duodenum, a hiatal hernia, and at times the lowest part of the esophagus and occasionally in coronary insufficiency. However, the location of visceral pain is of some value in determining the location of the lesion in the longitudinal axis of the trunk. In figure 2*a* and *b*, it can be seen that usually the nonperforating upper abdominal lesions produce pain in the epigastrium; those of the small bowel and appendix produce it in the periumbilical region and, similarly, those of the large bowel tend to cause the lowest abdominal pain.

When a visceral lesion penetrates enough to involve the serosa and secondarily the somatic

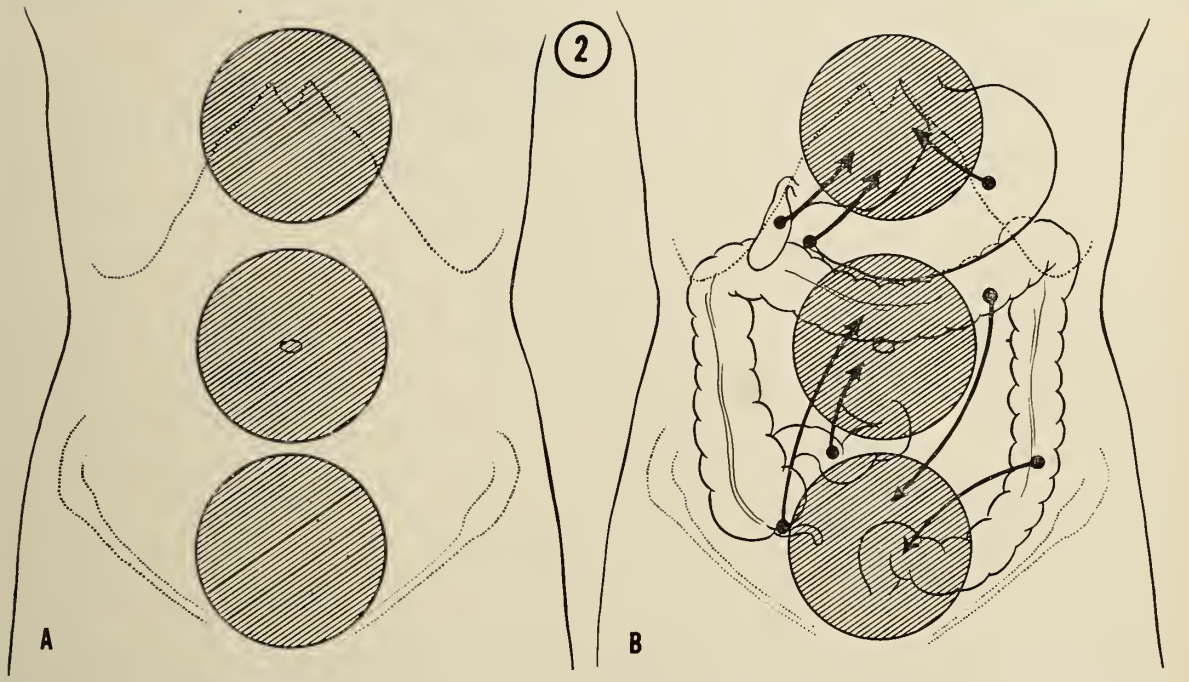


Fig. 2*a*. Three zones of pain from abdominal viscera. *b*. Pain of lesions in abdominal viscera tends to be referred to midline. Black dots indicate lesions.

pathways of the parietal peritoneum, lateralization of the lesion becomes possible. In most instances, the combination of the lateralized pain and the tenderness or pain on rebound will point to the organ involved and indicate which tissues have been involved. Analysis of initial visceral pain and subsequent development of somatic pain may outline the course of the lesion. Thus, the initial pain of gastric ulcer may be in the midline of the epigastrium, while the somatic pain resulting from perforation into the lesser omental tissues may be perceived only in the interscapular region posteriorly and may overshadow the visceral component.

PAIN OF PEPTIC ULCER

Application of these principles to the pain patterns of upper abdominal lesions helps in accurate diagnosis. Review of the different syndromes caused by peptic ulcer has led to the impression that they can be separated into five distinct groups resulting from pathologic changes.

Type 1, the visceral syndrome of pain (figure 3*a*) without referred pain occurs in ulcer when the ulcer has involved the mucosa or submucosa but has not penetrated sufficiently to involve the serosa of the stomach or duodenum. Only the splanchnic pathways are involved. A large percentage of the uncomplicated duodenal ulcers have this type of pain. The patient may present a so-called typical ulcer story with epigastric pain occurring several hours after meals and at 12 midnight to 2 o'clock in the mornings at the peak of the secretion of hydrochloric acid.

Pain of type 2 is visceral pain of ulcer with referred pain (summation syndrome; figure 3*b*). Pain of this type for example is produced by duodenal ulcers in which increased depth or progressive inflammatory reaction causes spasm sufficient to "spill over" to the corresponding somatic pathways, usually the seventh and eighth dermatomes on the right, at the peak of the pain. Before the peak is reached and after the peak has passed, the visceral pain remains in its initial midline epigastric location and is not shifted to the right portion of thorax.

Pain of type 3 (figure 4*a*) is an admixture of visceral and somatic syndromes in which the pain pattern contains both an intermittent visceral element and a continuous somatic element. When this occurs in duodenal ulcer, the pain is perceived continuously in the right seventh and eighth dermatomes as well as periodically in the epigastrium. The quality of the two types of pain is dissimilar, but in general they occur or are increased simultaneously and for that reason may be recognizable as of the same origin.

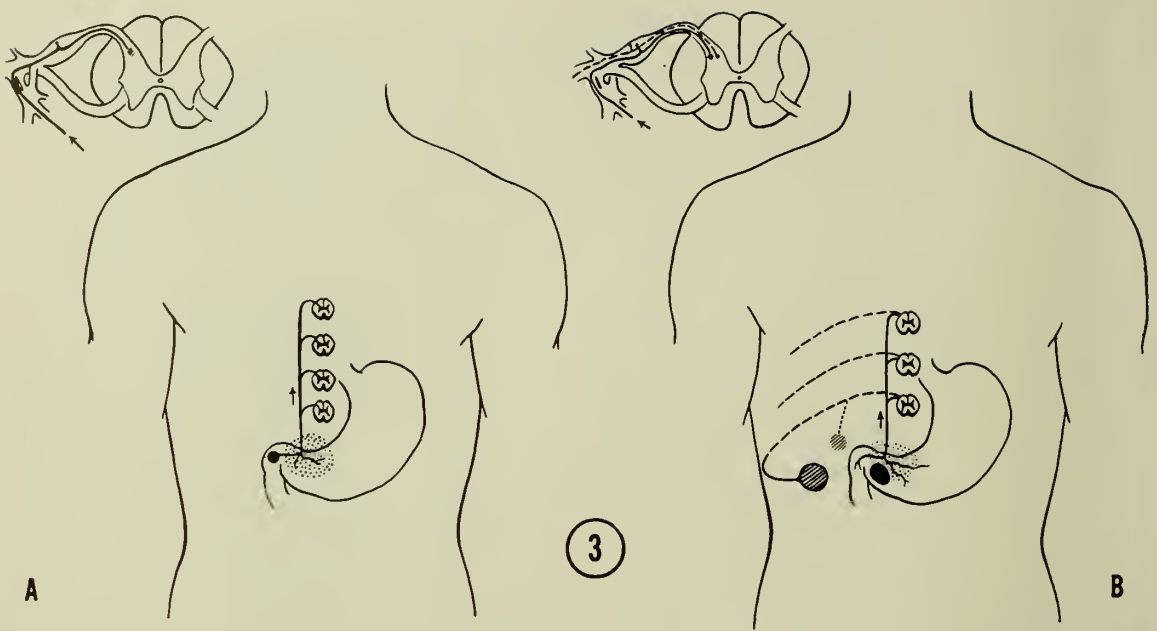


Fig. 3*a*. Pattern of pain of uncomplicated ulcer. Visceral pain only is present. Stippled area shows site of pain. The black dot represents duodenal ulcer. The arrow indcates the course of the splanchnic fibers with distribution from the sympathetic trunks to several of the segments of the cord. The diagram in the left upper corner shows the afferent visceral pain fibers passing from the splanchnic nerves through the white rami communicantes to the unipolar sympathetic cell bodies in the dorsal root ganglion, and from there into the dorsal horn of the cord. *b*. Pattern of pain when secondary visceralpain is present or somatic pain or both is produced only at the peak of the visceral pain. Visceral pain indicated by stippled area and splanchnic pathways are same as in *a*. The somatic pathway is also involved at height of the pain in the anterior right costal region as indicated by the dark-hatched area and in the posterior lower thoracic region as indicated by the light-hatched area.

This type of pain occurs when an ulcer invades the serosa of the duodenum, and a similar shift to the left may occur when the ulcer is gastric in origin. The addition of the somatic pain may confuse the patient with duodenal ulcer since the difference in the quality of the pain may convince him that it is the result of something new. Frequently, this conviction leads to a suspicion of gallbladder disease which so commonly gives pain in the eighth thoracic dermatome. The sec-

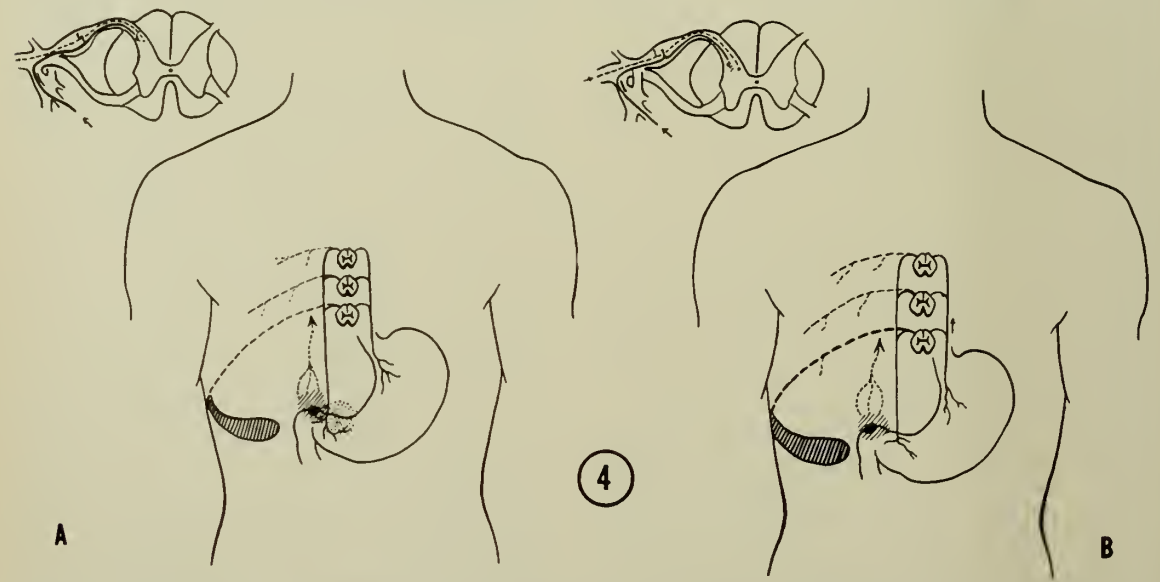


Fig. 4*a*. Visceral and somatic pain present continuously from duodenal ulcer. Black dot indicates ulcer, which is shown to be perforating by the free hatching around it. The dotted arrow indicates the means by which somatic pathways may be reached. The epigastric visceral component is the same as figure 3*a* and *b*. *b*. Somatic pain only. Visceral component has been lost.

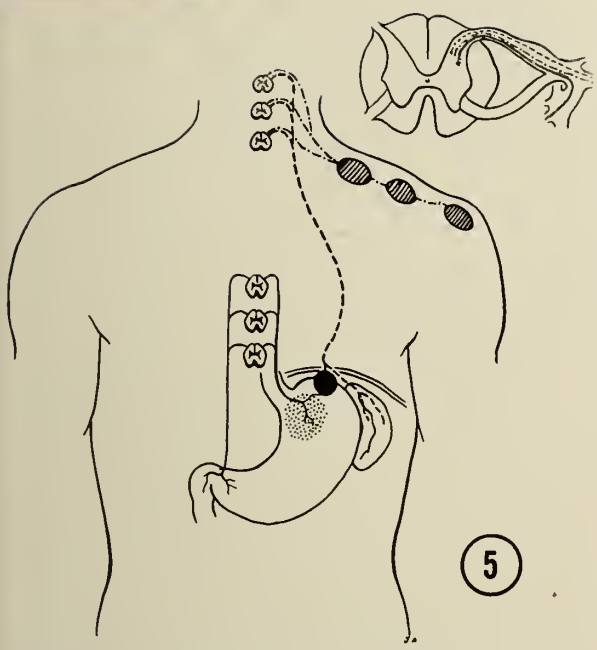


Fig. 5. Phrenic type of pain. Black dot indicates site of penetrating gastric ulcer. Stippled area shows visceral pain in epigastrium. The phrenic pathway extends from the diaphragm to the cervical region. The hatched areas on the left upper border indicate the sites to which this pain may extend.

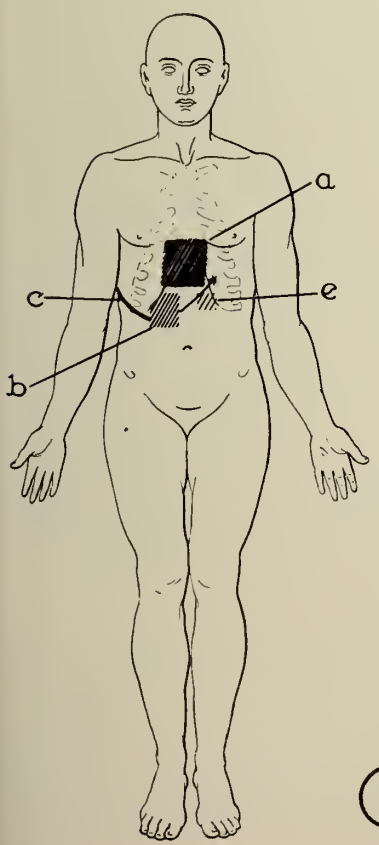
ondary involvement of the somatic pathway by the penetration of the ulcer may give rise to pain which is so severe that narcotics will be required for relief.

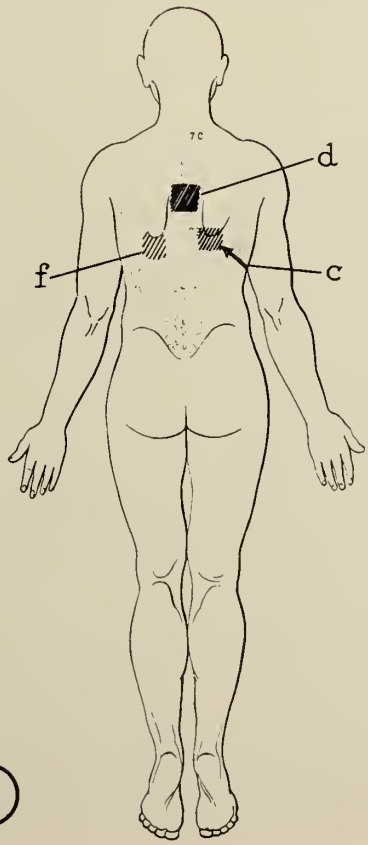
Pain of the fourth type consists of the somatic syndrome in ulcer with obliteration of the visceral syndrome (figure 4*b*). This type of pain occurs when the somatic portion of the pain pattern such as is present in type 3, becomes so strong that the patient notices only the somatic pain and ignores the visceral pain. This pain may be localized so far out and may occur so often at night that the individual may be suspected of having other conditions such as a cord tumor. At times the nature of the lesion can be proved only by surgical exploration.

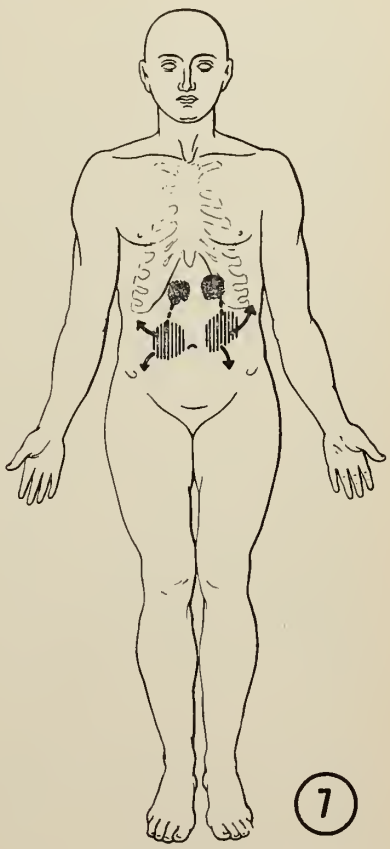
The fifth type of pain or the phrenic syndrome of ulcer is of somatic origin but involves a special nerve pathway (figure 5). The phrenic pathway extends to the third, fourth, and fifth cer-

Fig. 6. Disease of the gallbladder. *a*. Splanchnic pain as a result of spasm of gallbladder. *b*. Tenderness indicative of involvement of serosa of gallbladder as in acute cholecystitis. *c*. Pain of cholecystic disease is commonly projected to the right scapula. *d*. Projection of pain in some cases when cystic duct is obstructed or hydrops is present. *e*. and *f*. Unusual site and projection of pain in cholecystic disease.

Fig. 7. Pain of pancreatitis.







vical nerves. It is involved when the dome of the diaphragm is affected by perforation of ulcer or malignant lesion of the fundus of the stomach or by inflammatory reaction surrounding such perforation. The portion of each hemidiaphragm in the dome is supplied by the phrenic nerve while the periphery is supplied by the segmental spinal nerves, usually the lower six thoracic nerves. Both the phrenic and the segmental pathways may be involved and in such an instance pain may be interpreted as arising from the left side of the epigastrium and in the left shoulder.

Certain differences in the pain patterns of duodenal and gastric ulcers are explained easily when the innervation of the contiguous structures involved in perforation is considered. For example, in duodenal ulcer localized perforation to the pancreas is common when the ulcer is situated on the posterior wall of the duodenum, whereas an ulcer situated superiorly and laterally is more likely to involve the lesser omentum or the hepatoduodenal ligament. Uncommonly, even the perirenal tissues and the base of the mesocolon may be involved by perforating duodenal ulcer, and when this happens pain may be referred as in other renal or perirenal conditions or the pain pattern may include a right lower quadrant component which may be confusing enough to lead to appendectomy. Furthermore, the close proximity of the base of the gallbladder to the lateral aspect of the duodenum leads to confusion between lesions of these two structures. A right shift of pain along these pathways is sufficient indication for investigation of both the gallbladder and the duodenum in such an individual. Perforation of a peptic ulcer to the pancreas usually causes pain posteriorly from the tenth thoracic to the second lumbar vertebra. This pain may be lateralized to the right side of the spinal column in perforating duodenal ulcer or to the left side in perforating gastric ulcer.

In some instances perforation to the base of the gallbladder and to the lesser omental tissues may be felt only as a somatic pain without a visceral component (type 4) in the interscapular region at the level of the sixth or seventh thoracic dermatomes. To have type 5 pain when the phrenic pathway is involved is extraordinary in perforating or chronically perforated duodenal ulcers, although this occurs commonly during acute free perforation of peptic ulcers. It is not uncommon for type 5 pain to occur with transmission to the left shoulder or even to the left arm when the left hemidiaphragm is involved. The difference in frequency of type 5 pain on the two sides is merely the result of the fact that perforating lesions on the left can reach the diaphragm more easily than can perforating lesions of the duodenum. It is possible for the right phrenic pathway to be involved in the 5 per cent of patients in whom phrenic fibers find their way to the hepatoduodenal ligament.

When chronic perforation of a gastric ulcer, either benign or malignant, involves the lesser omentum, the undersurface of the liver, the lesser peritoneal sac, or the pancreas, the left half of the dome of the diaphragm, the spleen, the mesocolon, and the colon, it is because of the anatomic arrangement of these organs. Most benign gastric ulcers are just posterior to the lesser curvature of the stomach and because of this most frequently involve the lesser omentum, the liver, the lesser peritoneal sac, or the pancreas. Such an ulcer initially produces its pain in the epigastrium, either in the midline or slightly to the left of the midline, but when penetration or perforation occurs, the pain shifts to the left, either up into the left anterior portion of the thorax, into the retrosternal region, or from the left side of the epigastrium around or through to the left subscapular region. The malignant lesions of the stomach commonly involve the pancreas, the dome of the diaphragm on the left side, the perisplenic tissues, or the mesocolon and the colon. Perforation may give rise to pain which is located on the left side and may extend from the left supraclavicular region for the highest lesions to the left lower quadrant of the abdomen when the lesions involve the mesocolon. The perforating gastric ulcer which may occur in conjunction with an esophageal hiatal hernia, or the fundic lesion, which is commonly malignant, may give rise to pain which is located only in the thorax. The gastric location of the lesion may not be suspected unless knowledge of the pain pattern is available to the examiner.

PAIN OF GALLBLADDER DISEASE

When the pain patterns of gallbladder disease are considered according to our knowledge of visceral and somatic pathways, they can be grouped in a fashion similar to those of peptic ulcer. It is well known that chronic cholecystitis with stones may be entirely silent. However, if

obstruction of the cystic duct occurs, the pain changes according to the severity of the obstruction and the ensuing effect on the wall of the gallbladder. Prior to such obstruction the only symptoms may be pain of type 1 (figure 6, see *a*) with visceral pain limited to the infraxiphoid region or high in the epigastrium in a midline location. The only story may be that of qualitative dyspepsia for fats or of mild to severe colicky pain high in the epigastrium, usually of brief duration. This pain probably results from transient spasm of the cystic duct due to a stone or from transient obstruction with prompt subsequent relief of bile pressure. The gallbladder does not become inflamed, the serosa is not involved, and a shift of pain does not occur. Pain of type 2 (figure 6, see *b* and *c*) is one step farther in the process and represents summation as seen in a severe gallbladder colic during which pain, which has remained epigastric for a short time, may spread to the right, even as far as the right subscapular region during the peak of the pain.

When the somatic pain represented by residual tenderness is accompanied by visceral pain of type 1 or 2 (summation pain), it constitutes a mixture of type 3 (figure 6, see *b*) pain. Residual tenderness over the gallbladder may be great or it may be eliminated by the greater omentum which has no somatic pain fibers and is capable of separating the inflamed gallbladder from the parietal peritoneum.

When gallbladder disease has been present for some time or in infrequent instances in which there is no known previous disease of the gallbladder, obstruction of the cystic duct may give rise to pain of type 4 (figure 6, see *d*) which is felt only in the somatic pathways, either in the right subscapular region or in the interscapular region about the level of the sixth or seventh dermatomes.

Gallbladder pain of type 5 is uncommon but may occur in the patient with gallbladder disease who happens to be one of the 5 per cent in whom the right phrenic nerve supplies the hepatoduodenal ligament and the lesser omental tissues. Finally, the pain pattern of gallbladder disease would not be complete if pain on the left side were not mentioned. This has been estimated as occurring in 3 to 5 per cent of patients with gallbladder disease. It may be present in the left side of the epigastrium, or hypochondrium, or in the left subscapular region. When present, it may occur with or without an epigastric component. It may or may not be blamed on associated pancreatitis.

PANCREATIC PAIN

Pancreatic pain is unique in its behavior because it originates in an organ which has bilateral splanchnic innervation (figure 7). In addition, the pancreas spreads across the abdomen and is in close proximity to most of the upper abdominal organs. It is retroperitoneal, and its anterior surface is covered by a layer of peritoneum which blends with the anterior layer of the transverse mesocolon. Lesions which involve the pancreas may be localized, may be infiltrative, or may cause rather widespread diffusion of pancreatic enzymes. The patterns of pain are naturally dependent on the site of the lesion, that is, whether in the head, the body, or the tail of the pancreas. The pain also may be dependent on the nature of the lesion, that is, whether it is localized as in some forms of pancreatitis or due to involvement by the base of a perforating ulcer. If the pancreatitis is diffuse, severe pancreatic fat necrosis may be widespread, and the usual pain pattern may be obliterated.

The usual features of the pain pattern of pancreatic lesions are posterior location, exacerbation at night and when the patient is supine, and relief when the trunk is flexed or pressure applied to the epigastrium. The pain is usually persistent and, typically in chronic relapsing pancreatitis, its duration may be several days. Pain is usually severe and requires narcotics for relief. If the lesion is localized to the head of the pancreas, the pain may be unilateral and felt only in the right side of the epigastrium or to the right of the spinal column or in both sites. If the lesion is localized to the tail of the pancreas, the pain may be limited to the left side of the trunk, front and back. If the process is diffuse or if it involves only the body of the pancreas, the pain may be midline, usually posterior and in some instances anterior or encircling the trunk. When pain is present anteriorly, it is usually in the lower part of the epigastrium, and when present posteriorly it is usually between the level of the tenth thoracic and the second lumbar vertebrae.

Figures through 7 reprinted from Smith, L. A. and Rivers, A. B.: Peptic Ulcer: Pain Patterns, Diagnosis and Medical Treatment. New York, Appleton-Century-Crofts, Inc., 1953.

Pain from the Standpoint of Physical Medicine

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In assessing the value of physical medicine in the management of painful conditions we must define just what therapeutic means are available and how they can be expected to alter conditions to such an extent as to give relief of pain. It is essential, too, that we have some clear idea as to the basic mechanisms of pain in order that we may approach the problem of therapy intelligently. An attempt to understand these physiologic principles in regard to pain has been the goal of many investigators and yet we are still in the realm of hypothesis only; more study is needed before the explanations and theories can be accepted as fact. We can, however, arrive at a logical working hypothesis on the basis of what is now known.

Much animal experimentation on the pathways of pain and the effects of various agents upon painful stimuli is now a matter of record. Through the use of the newer electronic devices and technics, recent researchers have generally come to accept the theory that pain is conducted in the peripheral nerves by fibers called "A" and "C." The classification of the fibers on the basis of their physiologic functions handily fits into their anatomic divisions. It has been found that, depending on the nerve being studied, the ratio of unmyelinated to myelinated fibers is about 4:1. Gasser[1] used analysis of the electric response of mixed nerves and found that the largest afferent fibers, those varying between 10 and 20 microns in diameter, conducted most rapidly and were chiefly concerned with tactile and muscular sensation but not with pain. If these larger elements are excluded, many smaller ones remain which are myelinated and which range from 6 down to 2 or 3 microns in diameter. There remain also unmyelinated fibers averaging less than 1 micron in diameter. Fibers of both of these groups can transmit painful stimuli.

By observation of the characteristics of the action potentials of the various nerves, it is possible to separate the sensory nerves into alpha, beta, gamma and delta fibers, or fiber groups. This specialized field of study is within the province of the physiologist, and it is sufficient for our purposes to mention that recent work on the effect of ultrasonic energy on sensory nerves indicates that nerves can be destroyed and conduction can be suppressed. Sensory fibers can be damaged by means of ultrasonic energy but only after irreparable damage has been done to motor fibers. While doing this work, Treanor[2] noticed that when the beam of ultrasonic radiation was directed upon a conducting nerve, much of the "background static" (which possibly might represent true action potential) was eliminated as the temperature started to rise a fraction of a degree, before any recognizable damage to the nerve took place. This finding may be of significance if these small "impulses" represent nerve impulses, conceivably painful ones.

Studies of the asphyxiated or anoxic fibers disclosed that the medullated fibers lose their ability to conduct stimuli and that the larger fibers have the longest survival times. However, after all the medullated fibers are blocked, the nonmedullated C fibers are still functioning. In contrast, cocaine affects the nonmyelinated C fibers first and then proceeds to block the myelinated fibers in the same manner as does asphyxia. In cocaine anesthesia, slow pain im-

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pulses are blocked before fast pain impulses, while in blocking by asphyxia the reverse is true, lending support to the thesis that slow pain impulses are carried in the C fibers and fast pain impulses in the A fibers.

The researches of Wolff and his associates have brought much light to bear on the entire problem of pain and man's reaction to it. They divide the problem conveniently into two components, perception of pain and reaction to pain. Wolff has been able to quantitate man's perception of painful stimuli, and by use of his technics laboratory investigation of pain in man, with reproducible results, has been made possible. However, when faced with the enigma of man's reaction to pain, we recognize immediately that this is an extremely variable quality, related to climate, temperature, general state of health and mental attitude and mood of the patient under study. Recognition of all of these elements is essential to the proper approach to the treatment of pain.

Sherrington's original suggestion that pain was the body's signal for protective action is acceptable, but we must pursue the problem further. Pain serves a useful purpose up to a point, but after the need for protective reflex activity is gone, continuing pain does not serve a useful end.

It is quite generally agreed that pain is caused by a disturbance at sensory nerve endings or in the body of the nerve. This disturbance, chemical or physical, causes a break in the continuity of the cell membrane and sets up a stimulus along the afferent pathways to the brain centers involved. The stimulus seems to be related in a gross way to the speed with which the change at the nerve ending takes place. Thus, when trauma occurs suddenly, as from a bullet wound, one may feel little or no immediate pain. Then, too, if the change occurs ever so slowly, as in the case of slow freezing from exposure to the elements, pain may be absent. The majority of the problems of pain which come to the physician fall between these two extremes and the pain is usually chronic or subacute.

It was formerly believed that muscular spasm was the cause of many painful complaints. Clinicians would feel the tight bulging muscle present in strain of the lower part of the back and assume that the muscle was in spasm. It has been shown though, by use of the electromyograph, that we must be more discreet in our employment of the word "spasm." Harell, Mead and Mueller[3] clearly stated the definition as follows: "Spasm in skeletal muscle is a reversible state of sustained, involuntary contraction, accompanied by muscular shortening and associated with electrical potential changes." They went on to state that as far as the muscle itself is concerned, spasm is normal contraction. In 42 patients with low back pain, many had a list of the body and elevated muscle contours on the shortened side (supposedly contracted). However, electromyograms showed action potentials on the convex side (opposite to the list) and the supposedly painful contracted muscles on the concave side were electrically silent. Of 100 patients having poliomyelitis only 2 had spasm and this was not painful. So it would seem that spasm as such is not painful; moreover, when ischemic pain or pain caused by the injection of hypertonic saline solution into muscle was investigated, the associated muscles were electromyographically inactive. This work was in support of work done by North and Saunders[4] in New Zealand and agreed in general with their findings. Some technical difficulty arises in interpreting the results of electromyography but it seems that one must now look for something other than spasm to explain some of the painful syndromes.

It is probable that physicochemical changes which may stimulate the nerve endings directly or make them more susceptible to stimuli are in a rather delicate balance and thus quite sensitive to changes in local circulation. Experiments as cited by Kellgren and Shields[5] have shown that, of lesions causing pain in an area which could be studied conveniently, acute closed infections were the most dramatically affected by changes in circulation. Local changes in flow of blood have been measured in the knee and it is of interest to note that by raising the temperature only 5° C., one can produce a threefold increase in the flow of blood.[5] Studies of extremities show increase in flow of blood with increase in temperature.

Nerve injuries and glomus tumors are examples of changes in the nerves themselves which were studied and seemed to be completely unaffected by changes in the circulation. The various rheumatic disorders did not seem to be as much affected by local changes in flow of blood as were acute infections, sprains and fractures. This may be due to the fact that the changes existent here are chiefly concerned with the macromolecular connective-tissue substances

such as the collagen group and the polysaccharides which do not readily pass in and out of the blood stream.

Experiments done by Wells[6] on himself suggested that the type of pain that he produced, namely, pressure pain by means of an artery clamp on the web of the finger, is alleviated by the use of heat even though the blood supply is temporarily interrupted by means of a blood pressure cuff inflated to more than 200 mm. of mercury. He found, too, that any thermal gradient sufficiently steep, regardless of direction, could elicit pain. Wells said that changing the temperature gradient between the deep and superficial tissues, reducing the inequality, could be very effective in causing relief of pain. However, pain here was due to local trauma and not necessarily to the gradual accumulation of the irritating products of catabolism which seem to be more logically affected by actual change in flow of blood. Naturally, Wells' observations were based on only 1 case and there is need for much additional work for confirmation and elucidation.

Sensory end organs for pain are spread throughout virtually all of the tissues of the body. Three kinds of pain are recognized and designated: (1) superficial or cutaneous pain, (2) deep pain, from muscles, tendons, fascia and joints, and (3) visceral pain. The first two together form somatic pain and it is this type of pain which is amenable to treatment by the use of physical agents.

THERAPEUTIC AGENTS AND PROCEDURES

The physiatrist has many technics available to him for the treatment of painful syndromes. These involve the use of various physical agents or procedures, all directed toward the application of the various physiologic principles just discussed. A consideration of the use of roentgen rays and radium will be omitted as these physical agents are within the province of the roentgenologist and radiologist.

Rest. Rest is a physical agent which may produce reduction of afferent stimuli by diminishing activity. Also, reduction of the metabolic requirements of an affected part by resting it may reduce vascular engorgement which might be responsible at least in part for pain.

Heat (applied locally). Several forms of heat are used to relieve pain and each has certain advantages and indications. The effectiveness of heat in relieving pain has been attributed to increasing blood flow which heat does seem to do,[7] thus increasing oxygen available and carrying away any noxious chemicals. The application of radiant heat by means of electric light bulbs is an efficient means of producing surface heating. Various directors, reflectors, hoods or coverings are employed to concentrate and confine the heat to the part under treatment. Infrared sources of heat are readily available and most infrared lamps obtained at retail drug counters provide satisfactory spot heating. These small lamps are not effective for heating large areas such as the back.

Diathermy (long wave, short wave or microwave) is an excellent source of heat, especially for the deeper tissues. The recent ruling of the Federal Communications Commission, of course, limits these machines after July 1, 1952, to types which produce radiation that is confined to certain specified narrow bands. After this date, a physician will be permitted to employ only diathermy machines which have "'type approval" by this commission.

Ultrasonic energy, when employed medically, probably exerts its effect by means of raising the temperature of the tissues. This medium has been used more extensively in Europe than in the United States and great claims as to its effectiveness in such conditions as rheumatoid spondylitis, sciatica and lumbago have been made. In the United States, such claims have not been voiced so loudly and at present ultrasonic diathermy is relegated to the ranks of one of the less well-known means of heating tissues. However, much research is being done both here and abroad and out of these studies may emerge a better understanding of its mechanisms and usefulness.

Heat (applied generally). Heat applied generally in a fever cabinet has been effective in the hands of some investigators in treatment of the pain of acute rheumatic fever; when the rectal temperature was raised to 105 or 106° F. for a short time it produced variable relief of pain in some cases.

Counterirritants. The use of counterirritation by applying locally irritating medications seems to be confined chiefly to the athletic room and even there it is giving way to the use of more efficient and predictable heat lamps and diathermy machines.

Conductive heating. The use of paraffin baths for producing more prolonged heating of the extremities or paraffin applied in the form of a

painted-on pack to flat areas causes a good and fairly prolonged erythema.

Reflex vasodilatation is of some benefit in treating the pain due to occlusive arterial disease. Thus, heating the hands will cause some vasodilatation in the legs provided the disease has not progressed too far.

Massage. The two chief types of massage are sedative and stimulating. The stimulating type of massage is rarely used therapeutically today and has no place among our aids for relief of pain. The sedative type of massage is employed extensively, however. This consists of smooth, firm, rhythmic stroking and kneading applied to the skin and underlying tissues. An attempt is made to obtain muscular relaxation; hence, co-operation of the patient is very helpful. The work done by Randall, Imig and Hines[8] indicated that this type of massage does little to increase the flow of blood to any particular part, although they did show that passive stretching did significantly increase the flow of blood. According to Copeman, massage may exert its beneficial effects by breaking up numerous small pads of herniated fat in the fascia, some of which may have acted as trigger points of pain.

Hydrotherapy. The use of water, usually in motion, is helpful in acute injuries to extremities. Contrast baths are especially helpful in treating osteoarthritis of the hands and feet. The use of the whirlpool bath seems to relax the muscles of the extremity which is immersed and to produce some relief of pain.

Manipulation. At times it is helpful to resort to manipulation for the relief of pain. A good example is the use of pressure and stretching in reducing the slight dislocations that may take place in the vertebral facets, causing acute severe pain in the back. The use of stretching or traction of the cervical portion of the spinal column for pain due to nerve root pressure caused by cervical hypertrophic arthritis or for neuritis due to protruded intervertebral disk or to a narrowing of an intervertebral foramen is quite helpful and often is dramatically effective in relieving symptoms.

Exercise. The proper co-ordination of muscular actions and the training of weakened muscles to resume more nearly normal activity may often relieve pain or prevent painful conditions resulting from injudicious use of injured or weakened muscles.

Other physical agents. The application of cold packs or ice bags is often effective in relieving pain during the acute stages of sprains and strains and its analgesic effect seems to stem from two properties: (1) that of constriction of local blood vessels with resulting reduction in the amount of congestion and (2) the direct sedative effect upon the nerves themselves. This latter property is made use of in refrigeration anesthesia.

Application of the direct electric current is sometimes recommended as a means of relieving pain; however, there are many simpler and less complicated methods of relieving pain which are more effective.

Intermittent venous occlusion is still occasionally tried in the management of the pain of peripheral vascular insufficiency but has not been very helpful in our experience.

COMMENT

Pain as a symptom seems to arise from certain changes, probably a combination of physical and chemical changes occurring at or near the endings of the sensory nerves. Instantaneously perceived pain is primarily a beneficial sensation although patients with congenital indifference to pain seem to have little difficulty in dealing with the ordinary problems of life. The beneficial effect of instantaneously perceived pain stems from the body's reflex activity following the recognition of the painful stimulus. However, after the need for the protective reaction is gone, it is the pain which persists that becomes annoying, even damaging to the organism. For centuries, man has tried to be rid of these longer-lasting uncomfortable sensations and now physical medicine has joined with pharmacology in attempting to offer effective therapeutic means of combatting prolonged pain.

Chronic pain seems to have some dependency upon the adequacy of the blood supply and in particular the supply of oxygen to the affected region of the body. One convenient explanation of the pain of ischemic muscle is that there is an accumulation of some chemical agent which acts as the causative factor in producing the pain. Such pain in ischemic muscle then is relieved presumably during the recovery period by the removal of the irritant or its destruction by the presence of oxygen. In the specialized field of peripheral vascular disease, almost all of the pain which is encountered is considered to be due to ischemia. The types commonly observed can be classified as (1) pain of intermittent claudication, (2) rest pain, (3) pain of

ischemic neuritis and (4) pain of ulceration and gangrene.[9] Here general measures directed toward fostering collateral circulation and the prevention of excessive demands on the tissues of the affected region for more blood and oxygen are indicated.

Animal experimentation has given us a clear idea of the method of transmission of nerve impulses and recent studies on human volunteers have clarified our knowledge concerning man's reception and reaction to painful impulses. The search for more concrete evidence concerning the mechanism by which various agents produce relief of pain is continuing but at present we must be content with fairly broad generalities. We already know that heat is effective in relieving pain because it increases the flow of blood and thereby removes the agents which are causing the pain. But heat may be effective in relieving pain without any change in the velocity of the flow of blood; hence, there must be some other poorly understood factor coming into play.

It may still be convenient for the internist to tell the patient that the pain in his back is owing to spasm of the muscles but it has been shown that actually the muscles are not in spasm. However, heat, massage and postural exercises will make many patients having backache free of symptoms. Unfortunately, as yet, we are not sure just what physiologic principles have been active in producing this relief.

SUMMARY

Working along with the clinician, the physiatrist can do much to alleviate suffering. By judicious use of rest, heat, massage, hydrotherapy, manipulation and exercise, he can offer the patient immediate and prolonged relief of pain in a great many conditions. It is the application of known physiologic principles which provide the physiatrist with his technical aids, and recent studies have done much to clarify the reasons for their efficacy in any particular condition.

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PAIN AND SUFFERING

Since pain is felt as a blend of sensation, feeling tone, and individual response, both physical and mental factors must be considered. The site of stimulation may be anywhere along the pain neurons from skin to brain. In cutaneous tissues, pains are localized. But when deeper tissues are stimulated, sensitivity varies, localization is less certain, pain and tenderness appear where no stimulation exists, and activity is also aroused in remote parts.

Pain can be referred, as in toothache or ureteral colic; hallucinative, as in phantom limb; or symbolic, from mental stimulus. Nerve pathway pains are aggravated by coldness, dampness, fatigue, emotion, or stress.

Pain perception is intensified in unpleasant states of anger, fear, hunger, guilt, disgust, or grief and reduced in situations of joy or contentment or when distractions are present.

Boredom permits attention to small pains, and bodily threats or injury win attention and present pain in full intensity. Feeling tone can precede the stimulus if the painful situation is anticipated, thus mobilizing attention and displeasure around the sensation.

The object in diagnosis is to understand and know how to modify the pain sensation, feeling tone, and reaction. Accurate history-taking and comprehensive examination are important. Treatment aims at improving pain tolerance and reducing the provoking or aggravating factors from body or mind.

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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.*

MEASUREMENT AND EVALUATION OF PAIN

THE OPPORTUNITY to editorialize on the general subject of pain is welcomed. My experience is greatly in excess of my understanding of the consciousness of the individual who uses the term "pain" for a great variety of feelings that perturb, annoy, or terrorize. As usual the Greeks had a word for it "algesis" meaning sense of pain. This is a variant of the root "aesthesia" dealing with a sensation something short of pain. Hunger pain is mediated from the viscera to the inner consciousness in the same manner as pain of coronary inadequacy, illustrating how necessary it is to study grades of pain and all its association and variations.

Pain, or some discomfort, brings most patients to the internist. He would be greatly helped if he had some process to screen out the many with a low threshold of pain and with much emotional anxiety and constraint, and for whom in self defense, he is forced to provide much services, with laboratory and x-ray testing, for a primary pain analysis. After all the "negative" reports are assembled, the patient is often left with the presenting pain and an additional one has hit his pocketbook.

Cause and effect in any association of observed phenomena may easily invite error. Situations as tissue-rending as dissecting aortic aneurysm have been observed in which the subject alleged he felt no chest pain. When so much diagnostic evidence rests upon the subjective offering of pain, we should have more ways, direct or indirect, to measure the consciousness that proclains it.

Dietitians have suggested combining training and use of certain drugs to adjust the appestat in order to avoid obesity. Why not ask the anesthesiologist to develop a theoretical "algestadt" to raise or lower the pain threshold?.

My appeal to anesthesiologists to use the great opportunity offered in their daily work of inhibiting pain during surgery, stems from the unique position they occupy in the use of a large variety of pharmaceuticals—each exhibition becoming, in a sense, a psychological experiment. This is not an invitation for them to invade the fields of philosophy, theology, and psychology, even though within these disciplines are found countless sources of pain. There still remains, in the broad field of medicine, a wide latitude for collection of data and the study of the subconscious. Man without the subconscious would show little more inventive or creative genius than do the lower animals. The accumulated debris from memory's insults and scars, incidental to the strife of living, is part of the price man pays for his consciousness.

It sometimes appears as if the public depended less upon the clinical judgement of the doctor than upon the pronouncements of his numerous mechanical gadgets. In self defense he begins by unlimbering his heaviest diagnostic equipment with the result that much negative evidence accumulates. Too few doctors are interested in acquiring skill in treating functional disorders or in coping with the emotional responses arising from physiological maladjustment.

For the inhibition of pain, safe and potent drugs are with us in abundance. No evidence is needed beyond that offered by an operating theater in daily action. The amount of each local or general anesthesic agent needed is, in a degree, a measurement of the susceptibility to pain. The public use of tons of acetylsalicylic acid yearly is excellent testimony to the effective action of a blocking agent between the individual's sensorium and his consciousness. Somewhere between putting people to sleep and their awakening, it should be possible to learn much about the content of the subconscious cistern from which excludes so much psychosomatic pain. The psychiatrist's use of a barbiturate with catharsis of the subconsious gives a hint of what could be done on a much broader scale with so-called normal subjects. It should not be assumed that this approach aims at the masking of pain, either for the doctor's convenience or the patient's comfort. The first use of potent steroids in pneumoma was followed by asymptomatic rupture of peptic ulcers and generalized bacteremia. To assemble lines of correlation in any study is a tedious process, but when enough experiences override, explanations through chance alone are minimized.

Greater knowledge of nervous tract relationships, myoneural junctions, and synapse control, has followed the exhibition of blocking agents than ever followed the minutest histologic appraisal of ganglia and nerve tracts. With this background in mind, I shall settle for a handy "algesisometer." It will be the first testing gadget to be used when the patient's loquaciousness meets up with the doctor's skepticism, lest the combined emotionalism of both invite disaster.

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Like a skilful physician, who, in a complicated and chronic disease, as he sees occasion, at one while allows his patient the moderate use of such things as please him, at another while gives him keen pains and drugs to work the cure. —PLUTARCH

Section on PAIN

Reviews of New Books

SOME PAPERS ON NITROUS OXIDE-OXYGEN ANESTHESIA by the late Elmer Isaac McKesson, M.D. (director of anesthesia, Lucas County Hospital; consulting anesthetist to Flower Hospital and Toledo Hospital; anesthetist to St. Vincent's Hospital, Toledo State Hospital and Toledo Dental Dispensary, past president of the National Anesthesia Research Society, The Interstate Association of Anesthetists and of the Academy of Medicine of Toledo and Lucas County; Fellow of the International College of Anesthetists and of the American Medical Association, etc.). Edited by K. C. McCarthy. Privately printed, 1953, 180 pages.

The editor, K. C. McCarthy, has dutifully collected and presented the key papers given by Dr. McKesson and has emphasized the principles that he taught. It is altogether fitting that many of these sound principles developed by Dr. McKesson in his practice should be brought to the attention of anesthesiologists who might easily have missed or overlooked his important contributions. This book should be read by all who practice anesthesiology.

John S. Lundy, M.D.

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THE PHARMACOLOGY OF ANESTHETIC DRUGS, by John Adriani, M.D., director, Department of Anesthesia, Charity Hospital of Louisiana, 1952. Third edition. Springfield, Illinois: Charles C Thomas. Price $9.50.

The volume is essentially a reference manual and fulfills its function admirably. The index numbers some twenty-six pages (about one sixth of the volume) and is most comprehensive. Twelve pages of source material serve as a guide to those interested in elaborating on the information contained in the text. The presentation of material in tabular and diagrammatic form, while it does not make for easy continuous reading, is well suited for quick reference.

The third revision includes discussions on curare and other relaxants, autonomic drugs, vasoconstrictors and analeptics. Any deficiencies are those of omission rather than of commission, and these are doubtless due to the unavoidable time interval between revision and publication. It is regrettable that there is no discussion of succinylcholine as a relaxant; the use of n-allyl-normorphine in the treatment of opiate depression; hexamethonium and other ganglionic blockers and their function in modern day anesthetic practice; the use of ethyl and isopropyl alcohol in the treatment of acute pulmonary edema; plasma expanders and their uses. Further, since the realm of the anesthesiologist is extending beyond the operating theater, a chapter on the principles and practice of resuscitation would be most welcome.

Nevertheless, the author has compressed a wealth of information into a relatively small space, and the book remains a standard and obligatory text. One has no hesitation in recommending it.

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MAN'S BACK, by Theodore A. Willis, M.D., 1953. Springfield, Illinois: Charles C Thomas. 161 pages, 125 illustrations. Price $7.50.

This book is a presentation of the author's opinions and experience in regard to the human back, and he has employed many roentgenograms and many photomicrographs to make his points. He has presented the anatomy of the back in the text and in the illustrations in such a way that the reader who has not had experiences similar to those of the author can learn much about the human back. Injuries to the back, postures and how they affect the back, how casts are applied, myelograms, and diseases of the back are discussed. Roentgenograms illustrate the findings and photomicrographs depict detailed lesions. Tumors of the back and scoliosis are discussed. Brief chapters on psychoneuroses and malingering, physical therapy and operations on the back conclude the book. This book should be very valuable in consideration of the problem of pain in the back.

John S. Lundy, M.D.

Current Literature on Pain

SURGICAL TREATMENT OF PAIN. John Morton, M.D. J. Michigan M. Soc. 51:213-215, 1952.

Intractable pain is treated directly by surgery only when the primary source of the pain cannot be removed. Examples of this situation are preterminal cancer, trigeminal neuralgia and chronic pancreatitis. Accurate application of knowledge of functional anatomy is used to control pain by intercepting the neural pathways which conduct sensory impulses from the source of irritation. The procedures of choice are:

1. *Peripheral nerve section* is rarely done. Most peripheral nerves serve a dual function – sensory and motor – and one hesitates to sacrifice the motor component. In addition peripheral nerves regenerate resulting in recurrence of pain, disagreeable paresthesias, painful neuromas and phantom phenomena.

2. *Rhizotomy* is the intraspinal severance of the dorsal spinal root between the spinal cord and the dorsal spinal ganglion. Only the sensory components of peripheral nerves are cut and regeneration cannot occur. Rhizotomy is effective only for somatic pain, not for visceral pain. Persistent pain in a thoracotomy wound is ideally treated by this procedure.

3. *Cordotomy* is severance of the dorsal and ventral spinothalamic tracts. The operation does not destroy the all-important proprioceptive senses and if performed in the cervical cord will alleviate high thoracic pain.

4. *Ablation of specific sensory cortex* is done occasionally to control phantom limb pain. The operation is performed under local anesthesia and the area of the brain stimulated to reproduce or increase the phantom pain. The area is then resected. Results of this procedure are as yet not conclusive.

5. *Thalamic destruction* is indicated for those patients whose ultimate prognosis is not good though life may be expected to continue for an indefinite time. If such

a patient is deeply addicted to drugs, or there is an extreme state of anxiety, tension or concern with pain, one of several methods for destruction of the anteromedial nucleus of the thalamus is employed.

6. Three specific types of neuralgia wherein the pain is most severe, unrelenting, usually progressively disabling and without known etiology are trigeminal neuralgia, glossopharyngeal neuralgia and sphenopalatine ganglion neuralgia. The pain of trigeminal neuralgia may be limited to the distribution of one, two, or all three branches of the nerve and the only permanent cure for the terrifying distress is section of the sensory root between the Gasserian ganglion and the point of entrance of the root into the pons. The operation is performed under local anesthesia and may be done regardless of the age of the patient.

Glossopharyngeal neuralgia is a less common disability and is permanently cured by the intracranial section of this tiny nerve as it passes from its meatus in the anterolateral wall of the posterior cranial fossa to the brain stem.

Sphenopalatine ganglion neuralgia is a definite entity cured by incision of the ganglion.

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STUDIES OF THE SPINAL CORD. 3. PATHWAYS FOR DEEP PAIN WITHIN THE SPINAL CORD AND BRAIN. Robert E. Yoss, Ph.D., M.D. Neurology 3:163-175, 1953.

The course of the central nervous system fiber tracts mediating deep pain has long been poorly understood. Despite the fact that the Achilles tendon and other tendons are frequently clinically tested, the precise neural transmission of pain originating here has not been known. The term, deep pain, signifies pain arising from deep somatic structures such as a tendon and should not be confused with visceral pain to which this term is often applied. This problem was approached experimentally by exposing the Achilles tendon of anesthetized monkeys. When the monkey regained consciousness, and while still restrained on the operating table, the isolated tendon was stimulated by pressure caused by clamping a rubber-tube-covered hemostat on the tendon. No response interpretable as pain was obtained when the animal was tested immediately on recovery from anesthesia. If, however, the wound was closed and the animal allowed 24 hours to recover from the anesthesia and then retested without anesthesia, a typical and conclusive response to pain was obtained.

In the monkey, impulses set up by painful stimulation of tendons ascend in the lateral spinothalamic tract of the spinal cord on the side opposite their origin. There is a pattern of localization within the lateral spinothalamic tract not only for fibers mediating impulses set up by superficial painful stimuli but also for fibers carrying impulses from the painful stimulation of tendons.

Impulses set up in the Achilles tendon by painful stimuli ascend in the most dorsolateral portion of the lateral spinothalamic tract on the side opposite from their origin. Painful stimuli from the wrist tendons are localized in the more ventromedial portion of this same contralateral spinothalamic tract.

No impulses from tendons which are interpreted as pain ascend in the dorsal white column of the same side. Also, in the monkey, deep pain reaches consciousness at subcortical levels, presumably in the dorsal thalamus.

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STUDIES ON PAIN: MEASUREMENTS OF ACHING PAIN THRESHOLD AND DISCRIMINATION OF DIFFERENCES IN INTENSITY OF ACHING PAIN. James D. Hardy, M.D., Harold G. Wolff, M.D., and Helen Goodell, M.D. J. Applied Phys. 5:247-255, 1952.

Aching pain arises from noxious stimulation of visceral and deep somatic structures and, therefore, is a pain quality of great diagnostic significance to the physician. One method of evoking aching pain is the application of pressure on the subcutaneous tissues of the forehead measuring the force in grams. By this method, the threshold for aching pain is found to be 357 ± 115 gm.

The difference threshold is determined by measuring the intensity of two stimuli evoking a just noticeable difference (jnd) in pain intensity. At threshold, the jnd is 125 gm. At 5200 gm. stimulus, the jnd is 1400 gm. Fourteen jnd's are observed in this stimulus range. However, fourteen jnd's are not ceiling pain. The amount of tissue damage produced by pressures of 6000 gm. or more makes it impractical to test beyond 14 jnd's.

Direct comparison of intensities of aching and pricking pains shows that pains of equal intensities in different modalities are above the threshold to the same extent *when measured in terms of the jnd.*

Measurement of aching pain is as precise as measurement of pricking pain, if data is expressed in terms of the jnd. Moreover, aching and pricking pains can be compared as regards intensity, and pains of equal intensity are above threshold by an equal number of jnds. The extent of the intensity dimensions for pricking and aching pains are roughly the same.

Experiments using 30 mg. of codeine and 40 mg. of meperidene show that, when results are expressed in jnd's, the effects of such centrally-acting analgesics on the threshold of one pain quality, e. g. aching pain, can be freely applied to the threshold of another pain quality, e. g. pricking pain.

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CERVICO-BRACHIAL PAIN. Robert W. Newman, M.D. South Dakota J. Med. and Pharm. 5:37-50, 1952.

Among several important characteristics of pain of nerve root origin is accentuation by stretching of the affected nerve root, and aggravation by increased intra-abdominal or intra-thoracic pressure. The increased pressure of coughing, sneezing or straining forces blood from the usual large local venous pool with engorgement of the numerous epidural veins. Traction on the involved nerve root produces pain following displacement of the dura by epidural venous distension.

LESIONS WITHIN THE SPINAL CORD OR SPINAL CANAL

Neoplasms of the cord are an infrequent cause of cervico-brachial pain. About 75 per cent of cord tumors are extramedullary and with these neoplasms prognosis is more favorable because of less extensive involvement of the central nervous system. X-rays may show destruction of a portion of vertebral bodies or widening of the intra-pedicular space.

Syringomyelia may produce pain of radicular nature but paresthesias are more common.

In *herpes zoster* slight paresthesia and hypersensitiveness are early signs in the area of the dermatome of involvement. Burning, and frequently intense pain develops later.

Hypertrophic cervical pachymeningitis usually presents a symptom complex indistinguishable diagnostically from syringomyelia or intramedullary cord tumors. Positive serology indicating a luetic infection aids in diagnosis.

LESIONS OF THE VERTEBRAL COLUMN

In *herniation of a cervical intervertebral disc* pain with stiffness and soreness of the neck is usually the earliest sign, and pain becomes the dominant symptom in the shoulder, upper arm and forearm.

Rheumatoid and hypertrophic arthritis of the cervical spine may produce radicular pain by actual pressure from hypertrophic outgrowth, osteophytic encroachment of the neuroforamina, or diminution in diameter of the foramina following thinning of the intervertebral disc. Radicular pain may result from inflammatory involvement of periosteum, fascia or ligaments.

Tuberculosis of the cervical vertebrae is seldom seen today but produces severe, intractable pain of the deep, boring type.

Neoplasms of the cervical vertebrae are rare and more frequently metastatic than primary. Such tumors produce deep constant pain that is accentuated during recumbency.

The signs and symptoms of *basilar impression or platybasia* depend upon the amount of compression of local structures. This condition is usually distinguishable by x-ray studies.

LESIONS OUTSIDE THE VERTEBRAL COLUMN

Scalenus anticus: Contraction and hypertrophy of the scalenus anticus muscle may be secondary to brachial plexus irritation by pressure against the first rib due to a high sternus with an elevated first thoracic rib, a depressed or low placed shoulder girdle, or an abnormal brachial plexus, post fixed; or root irritation from protrusion of the cervical intervertebral disc and hypertrophic or rheumatoid cervical arthritis.

Cervical rib per se probably does not give rise to symptoms but provides a local anatomic condition favoring mechanical pressure on the subclavian artery and lower brachial plexus radicals.

The *costo-clavicular syndrome* is produced by intermittent compression of the subclavian vessels and the brachial plexus between the first thoracic rib and the clavicle; while the *hyperaduction* or *coraco-pectoral syndrome* is due to compression, during hyperaduction of the upper extremities, of the subclavian vessels and the brachial plexus between coracoid process of the scapula and pectoralis minor muscle.

Lesions of the shoulder joint: Painful, stiff shoulder, with pain local or radiating down the arm is related to the soft tissue structures about the scapulo-humeral joint. Calcium is deposited primarily in degenerated fibres of the fibrotendinous cuff, and the symptoms are probably secondary to involvement of the synovial lining of the subacromial bursa.

WHAT IS PAIN? W. K. Livingston, M.D. Scient. Am. 188:59-66, 1953.

Pain is a product of consciousness in which the essential element is awareness. In many instances pain is proportional to the injury. A concept of pain as a physical quantum, measurable in terms of stimulus intensity or the body's response to injury is an interpretation that is reasonable, but does not apply to many situations. Superficial wounds are more painful than deep ones because of the skin's more abundant sensory innervation.

Extensive individual variations in pain are easily demonstrated. Patients with causalgia, facial neuralgia, or postherpetic pain, in which the lightest touch induces severe pain represent one extreme. At the other, are children born without normal pain susceptibility who may lean against a hot stove without showing signs of distress.

Depression of brain function impairs pain perception. This nullifies any concept that either a dying person or one undergoing general anesthesia feels pain despite physical manifestations that are usually associated with pain.

Assessment of pain: Eliciting pain under controlled conditions, as by heat, electric current or pressure, shows that most normal persons have the same threshold for pain, although the tolerance to pain is highly variable. Most people feel pain when skin-applied heat reaches 220 millicalories per cm.^{2} per second. If such pain is endured until the burning point has been passed, the pain lessens because the burning process has destroyed the more superficial sensory fibers.

Conduction of pain: Pain is carried by two types of nerve fibers. Large myelinated fibers transmit "fast pain" described as "bright," "sharp" and "pricking." Slow pain, "lingering," "reverberating" and "burning," is conducted by small fibers with little or no covering of myelin.

Pain as protection: Muscular reflexes are the body's first line of defense against injury by frequently breaking contact with the offending stimulus.

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INTRAVENOUS INJECTION OF PROCAINE IN TREATMENT OF PRURITUS ANI. Lawrence G. Beinhauer, M.D., and Samuel R. Perrin, M.D. Pennsylvania M. J. 55:133-134, 1952.

Properly controlled, intravenous injection of procaine is a safe method for the treatment of pruritus ani. The procedure can be used for hospital or ambulatory patients.

The dosage used is 0.1 to 0.2 per cent procaine in 500 cc. of saline solution over a 45-minute period. Ascorbic acid, 200 mg., is added to each infusion, also 5 per cent glucose if edema is present. The treatment is done daily for six to twelve days. Relief is usually obtained after the fourth injection but, if not produced in six days, treatment is discontinued.

Of 60 patients with pruritus ani without a demonstrable cause, 17 obtained complete alleviation, 26 temporary benefit, and 17 no relief. The observation period extended from three weeks to one year.

Skin testing is utilized. Symptoms are aggravated if patients have myasthenia gravis or thyrotoxicosis, but these manifestations can be controlled by the addition of pentothal sodium to the infusion solution. Patients receiving digitalis or other glycoside should be carefully observed for evidence of digitalis intoxication before the administration of procaine.

Lancet Editorial

Educational Activities of the American College Health Association

PUBLIC INTEREST in medicine is always high but is probably more intense in recent years than has ever been true in the past. Churchill has stated that, "the quest for individual survival in this world is fully as intense as the older hope for personal immortality in the next."[1] The medical and allied professions have made enormous strides in easing the every day burdens of living and in prolonging life itself. Just to imagine the conditions under which the average citizen lived prior to the extensive use of anesthesia beginning in 1846 is to convince oneself that advances in medical knowledge are of prime importance as far as the comfort of the individual is concerned.

Dana L. Farnsworth, M.D.

This progress has not been without its disadvantages. The chief one is probably of an economic nature. As medical facilities, both therapeutic and preventive in nature, have become more effective and more complicated, they have likewise become more expensive, the increase being by geometric rather than arithmetic progression. Thus in a sense citizens must pay dearly for their added comfort, convenience and longevity. In another sense medicine is committing economic suicide unless it can find satisfactory ways of paying for its new developments. We have seen strong differences of opinion arise within the medical profession and between various factions within the country concerning the distribution and methods of payment for medical care. There are many who feel that movement in the direction of state medicine is the only way that medical care can be given fairly and adequately to all our people. There are others, apparently the majority at this time, who feel that progress in the direction of state medicine would be a serious mistake and who believe that extensive experimentation with voluntary health plans is the proper direction of emphasis for American medicine.

As medicine goes forward, it is vitally necessary for the medical education of the public to progress with equal thoroughness and rapidity. Nowhere can this be done with greater effectiveness than in our colleges. The citizen must learn how best to use a medical adviser, what he should do to protect himself through community and national health measures, and also how to pay for those essential services in such a way as not to be subject to catastrophic financial crises at times he is least able to meet them. The American College Health Association has as one of its main functions the diffusion of adequate and effective attitudes about medicine in order that students, who will be our future community leaders, will know how to use medical facilities to the greatest possible advantage and to cooperate in the most advantageous manner with the medical practitioners and scientists.

The Association itself is primarily devoted to furthering the education of its members in order that they may carry out their important tasks of health maintenance and restoration more effectively. About 225 institutions of college grade belong to it, and any individual who works in the health services of these institutions may be considered a part of its total membership. Educational procedures must include the efforts of all those interested in promoting health — physicians, nurses, health educators, physical education specialists, athletic coaches and trainers, social workers and others in sciences which contribute to medicine or health.

The objectives of an ideal health service have recently been formulated as follows:[2]

To promote individual and general health in the college community by means of a program of comprehensive medical care.

To prevent illness or injury when possible, in terms not only of sanitation and living conditions but also of factors promoting social and emotional maturity.

To serve as an educational center for the collection and dissemination of information that affects the health of the community; this includes the maintenance of a referral or consultation service to enable college personnel to make effective use of the medical resources of the community.

To aid in freeing the student or staff member from physical or emotional handicaps that prevent him from utilizing to the fullest extent the academic, extracurricular or environmental resources of the college.

To care for sick students or staff members.

In many colleges everything that has to do with the promotion of health is centralized in a medical department which coordinates the health educational activities of other departments. In other colleges

health promotion is carried on by several departments coordinated by means of health councils made up of representatives of participating departments, sometimes with student participation. There has been comparatively little participation by students in the planning and organization of their own health services in this country, though in some Scandinavian countries the students organize their own health services almost independently. Steps are being taken in this direction, notably at Leland Stanford University, with increased benefit to all concerned. It would appear that the more students can be encouraged to take part in the planning of the health service functions, the more likely they are to be intelligent leaders and planners in community health matters at a later period.

There are about 1800 institutions in the United States that give instruction of college grade. The variety of health services ranges from no service at all in many of the smaller institutions, to elaborate medical and health programs in the large universities, with full complements of all possible related professional personnel together with fully equipped hospitals. To lay down general principles of maintenance and operation of these services in such a wide variety of educational institutions is a most difficult task. It has been found profitable in the past to have periodic surveys of health practices all over the United States and Canada in order that advances made in one section might be made available to those in other parts of the country. There have been three such national conferences on health in colleges, the first in Syracuse, New York in 1931, the second in Washington, D.C., in 1936, and the third in New York City in 1947. After each conference the proceedings have been edited and published, thus serving as a guide for health planning for colleges for the next five to ten years. The Fourth National Conference on Health in Colleges will be held in New York City May 5, 6, 7, and 8, 1954, at the Hotel Statler. This Conference will be devoted to about 16 to 20 working seminars of 15 to 30 persons each, each group devoting itself to some aspect of student health policy, organization, or maintenance that is of acute interest at this time. Among the subjects which are at present planned as discussion topics are:

1. Administration, Organization and Function of a Medical Service
2. Training Programs in Student Medicine for Physicians and Nurses
3. Special Health Problems of Foreign Students
4. Insurance and Other Prepayment Plans
5. How Can Student Health Practices be Influenced through Health Education?
6. The Health or Medical Service as an Educational Agency
7. Community Resources Which Can Contribute to College Health
8. Physical Education and Recreation as a Health Agency
9. The Role of the College Health Nurse
10. The Dean of Students and the Health Program
11. Student Participation in Health Planning
12. Correlation of Counseling Functions in College
13. Research Programs
14. The Development of the College Mental Hygiene Program
15. Environment and Health
16. Student Health Records—Their Use and Misuse.

A permanent committee chairman has been selected for each of these seminars, and he will appoint others to aid him in the preparation of the detailed items to be considered in the conference room. There will be a few general correlating and summarizing sessions so that persons who attend will be aware of the thinking of other groups than those in which they participate individually. When the proceedings of all the committees have been edited and coordinated, they too will be published in book form to serve as an educational device in promoting the best possible standards of health in all institutions and individuals who are interested.

This Conference will be open to all those who have a stake in high health standards for college students, staff, and faculty members. It is hoped that in addition to professional personnel in this field, there will be a liberal representation of college presidents, deans, and some student leaders. President James L. Morrill of the University of Minnesota is president of the Conference, and the president of the American College Health Association is its chairman. Thus in effect the entire year's activity of the A.C.H.A. will be devoted to making the Fourth Conference a success. The chief sponsoring agency aside from the A.C.H.A. is the National Tuberculosis Association and in addition some 30 to 40 other national organizations vitally interested in student health will be invited to sponsor and participate actively in the proceedings of the Conference.

In these and other activities the American College Health Association hopes to do its full share in improving medical care for college students and in bringing the many advantages that medicine has to offer to all our people.

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The Stability of Income

One characteristic usually associated with a bond is that it has an established rate of interest; the investor therefore can compute the annual income he may expect from the date of purchase to the date of final maturity. A bond, like a note or mortgage, is a promise to pay a stipulated amount at a designated future date with interest to accrue in the meantime. This provides STABILITY OF INCOME—once a sound investment is made the annual income is fixed and is not altered by changing economic conditions or market fluctuations.

During the past several years, however, the STABILITY OF INCOME has been impaired by increasing Federal income taxes. The income that invested savings earn, when subject to such taxes, does not enjoy complete STABILITY OF INCOME since a change in the tax rate requires an adjustment in actual "spendable" income received—if taxes rise the effective income is reduced.

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Large Scale Rorschach Techniques: A Manual for the Group Rorschach and Multiple Choice Test. M. R. Harrower and M. E. Steiner, 1951, second edition, 353 pages. Charles C Thomas, Springfield, Illinois. Price $8.50.

The book is divided into six parts. Part I deals with the development of the Group Rorschach method, with directions for scoring and interpreting. Part II is an analysis of Group Rorschach materials in terms of location, determinants, and content. The main body of the book is contained in Part III, which consists of a Multiple Choice Rorschach test, derived from the material presented in Parts I and II, which can be used for rough screening purposes. Part IV reviews the recent developments in Group Rorschach techniques, with chapters referring to industry, hospitals, education, and the Armed Forces. Part V is an analysis of content, presented entirely by means of tables. The final part, VI, is a statistical study of "Card-Pull."

There are numerous charts and graphs giving normative data about the groups studied. In fact, almost a third of the book consists of these tables and graphs. Most of the figures are percentages, however, and very little is presented in the way of statistical analysis.

Another point to be kept in mind is that, while the authors state that their main concern in developing the Multiple Choice test is to provide norms for the college age group, this group consists mainly of medical students and nurses. As such, it does not present a very good sampling of college students. The authors themselves say that an occupation such as medicine does influence the Rorschach record. Furthermore, this college age group of 224 is contrasted with three other groups —"normal" adult males, psychotics and psychopathic personalities, and prison inmates. These other groups consisted of only 34, 41, and 41 persons, respectively, and none were equated for age, education, or other variables.

The section on card-pull gives, as does the rest of the book, normative data that should be of use to one using Group Rorschachs. However, one is disturbed that the authors' present material showing the differences between results of individual testing and group testing, with no discussion of it.

Although Large Scale Rorschach Techniques contributes a new test method and normative data for those using Group Rorschachs, one should be aware that it has serious defects involving statistical analysis as well as assumptions that go beyond the data.

Harriet Juckem

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Penicillin Decade Sensitizations and Toxicities, by Lawrence Weld Smith, M.D., medical director, Commercial Solvents Corporation, and Ann Dolan Walker, R.N., former editor of "Trained Nurse and Hospital Review," 1951. Washington, D. C.: Arundel Press, Inc.

This is an objective report of the principal published data on untoward effects of penicillin therapy over the first decade of its clinical use. While in an individual practice such effects may seem to be rare, the results of this investigation of reports of unfavorable reaction are surprising and even startling.

Outstanding are the number of allergic reactions, some severe and others even fatal. Reactions at first were chiefly pyrogenic due to impurities in the amorphous forms of penicillin; however, a certain number of patients always have shown a sensitivity to penicillin itself. Although with the appearance of crystalline penicillin G for clinical use, the reaction rate fell off sharply, it increased again as more and more patients during succeeding courses of penicillin therapy became sensitized to the antibiotic itself. With the introduction of procaine penicillin there was a striking reduction in reaction rate, but once again the recurrent use of procaine penicillin in the same patient caused reactions. It remains to be seen whether the new so-called hypoallergenic preparations will prove to be of value. In addition the trend of certain types of organisms, notably staphylococci, to show steadily increasing resistance to penicillin, has been noted. The contents of this review emphasize caution with regard to the use of penicillin or any antibiotic for minor infections and stresses the phyiscian's responsibility for sound clinical application.

C. A. McKinlay, M.D.

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Oestrogens and Neoplasia, Harold Burrows, and Eric Horning, 1952. Springfield, Illinois: Charles C. Thomas, 189 pages. $6.75.

This is a valuable book filled with information which cannot be easily obtained in other places. The first chapter will interest many men because it contains so much on the chemistry of estrogens. There is much on the influence of estrogens on tissue growth throughout the body, and also on the influence of estrogens in produicng cancer.

Those physicians who still feel that it is too dangerous to give estrogens to women should note that if the use of the estrogen is interrupted from time to time nothing is likely to happen because then, "The affected tissues will revert to their former healthy resting state." "Tumors will be produced only if the supplies of oestrogen have been incessant, or if the intervals between the supplies have been too short to permit a complete reversion." Hence it is that the authors advise against the use of implanted pellets of estrogen as their use might be dangerous.

It is interesting to learn that as early as 1896, Sir George Beatson removed both ovaries from a young woman who had general metastasis from a cancer of the breast. Eight months later all traces of carcinoma had disappeared. During the next few years this type of treatment was used fairly frequently, and some relief of symptoms was observed in about one-third of the cases.

One finds in this book much information also in regard to the estrogens which keep forming in some women after their ovaries have been removed.

The work of Huggins and his school on prostatic cancer goes back to 1940. Interestingly, John Hunter, between 1728 and 1793, was the first one to make a systematic study of the progressive atrophy of the prostate gland following castration. Then White, toward the end of the nineteenth century, proposed castration as a treatment for men suffering from benign hypertrophy of the prostate gland. Comprehensive papers on the results of such treatment were written by Wood in 1900 and White in 1904.

Walter C. Alvarez, M.D.

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News Briefs . . .

Dr. Ernest J. Larson, *Jamestown, was elected treasurer of the North Dakota State Medical Association at their sixty-sixth annual meeting in Minot.*

North Dakota

Closer cooperation between the North Dakota State Hospital at Jamestown and the various agencies of the State Public Welfare office was studied at a conference of the two state groups at Jamestown on August 14. The need for more psychiatric nursing personnel was stressed. At the present, nurses training in North Dakota must go out of the state to gain their required psychiatric training.

° ° ° °

A directory of services for handicapped persons in North Dakota was planned at the quarterly meeting of the Counselors Committee of agencies concerned with the welfare of handicapped children and adults held August 4 at Fargo.

° ° ° °

Eighteen diabetic children enjoyed a week of outdoor life at the first North Dakota Diabetic Children's Camp which was held at Turtle River State Park from August 9 to 16. It was sponsored by the North Dakota Diabetics Association and medical supervision was provided by eight doctors who each donated a day to the camp. They were Dr. T. Q. Benson, Dr. C. M. Graham and Dr. R. C. Turner of Grand Forks; Dr. N. A. Hardy, Minto; Dr. A. C. Kohlmeyer, Larimore; Dr. Martin Hochhauser, Garrison; Dr. Lester Wold and Dr. William A. Stafne, of Fargo.

° ° ° °

Plans for a new $30,000 clinic building are being drawn up at Tioga as the first step in Tioga's hospital program.

° ° ° °

Dr. W. F. Shiler, Devils Lake, was recently honored with fellowship in the International College of Surgeons.

° ° ° °

Dr. F. G. Hubbard, of Forman, was honored by the town of Mandan in commemoration of his fifty years in the medical profession. Present at the celebration were 150 of the 1,217 babies Dr. Hubbard delivered during his 50 years in Forman and Sargent county, as well as 1,000 friends and neighbors.

° ° ° °

Dr. O. W. Johnson, Rugby, was appointed by Governor Norman Brunsdale to membership in the state health council, succeeding Dr. W. A. Wright of Williston, for a term of three years.

° ° °

Dr. James A. Moses has opened offices in Richardton. A graduate of the University of North Dakota, Dr. Moses received his medical degree from Bowman-Gray Medical School, and has been practicing with the Quain and Ramstad clinic at Bismarck.

Three Winnipeg physicians have recently established practice in North Dakota. Dr. Paul V. Adams, formerly with the Winnipeg Clinic, has joined Dr. David Peterkin in practice at Langdon. Dr. J. D. Thordarson will be associated with Dr. W. S. Pollard of Maddock in the Benson County Clinic and Maddock Memorial hospital. Dr. J. E. Connor has opened an office in Cavalier in association with Dr. J. F. Johanson.

° ° ° °

Dr. Charles F. Schnee, Long Island, New York, a graduate of Mc Gill University, has joined the staff of the Garrison clinic as a general surgeon.

° ° ° °

Dr. John M. Van der Linde, New York City, has joined the Medical Arts Clinic at Jamestown. Dr. Van der Linde, a graduate of Long Island College of Medicine in 1941, specializes in internal medicine.

° ° ° °

Dr. Stuart J. Cook, Roland, Manitoba, has opened a practice in Rolette.

Minnesota

Twenty students have taken pre-medical work at the University of Minnesota Duluth Branch since the program was first offered in 1947, it was announced recently. Eighteen of these students have entered the University of Minnesota Medical School to complete their training.

° ° ° °

Ten physicians from the Mayo clinic were awarded silver medals for excellence of their exhibits at the convention of the American Medical Association. Cited for their showings on disease of the mitral valve were Doctors T. J. Dry, R. L. Parker, J. E. Edward, J. W. Kirklin, R. D. Pruitt, G. W. Daugherty, C. H. Schiefley, A. J. Bruwer, R. G. Tompkins and A. H. Bulbulian.

° ° ° °

The cornerstone laying ceremonies for Madison's new $500,000 hospital were held on Sunday, August 9. Taking part in the program were Dr. M. O. Sletten, president of the Madison Hospital Board, and Dr. Magnus Westby, chief of staff.

° ° ° °

A new clinic was opened in Rochester on August 24. Drs. H. A. Wente, James R. Doyle and John L. Stransky will staff the clinic, which will be known as the Olmsted medical group. The clinic itself is a one-story building with six treatment rooms in residential Rochester.

° ° ° °

Dr. Henry E. Michelson was chosen to give the William Allen Dusey oration before the Chicago Institute of Medicine on September 23. His subject was "A Review and an Appraisal of the Present Knowledge of Erythematosus."

° ° ° °

Methods of securing funds to continue the rural nurse training program in Minnesota are now being studied by a special committe representing some 40 hospitals administrators and nursing leaders from all parts of the state. The program was started as a demonstration project by the University School of Nursing in the early 1940's, and has been financed by the state board of nurse examiners, the W. K. Kellogg foundation, and by the

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Farm Bureau Women of Minnesota. Under the program, 14 urban nursing schools send their students to hospitals in six smaller communities for special training.

* * * *

MINIMUM FOOD NEEDS in cases of emergency is the subject of a new five-year research project at the University of Minnesota's Labratory of Physiological Hygiene. Nineteen soldiers from Fort Lee, Virginia have volunteered for the first of a series of experiments.

South Dakota

DR. R. G. MAYER, Aberdeen, is the new president of the South Dakota State Medical Association. Other officers elected at the annual meeting include Dr. A. W. Spiry, Mobridge, president elect; Dr. Floyd Gillis, Sr., Mitchell, vice president; and Dr. G. I. W. Cottam, Sioux Falls, secretary-treasurer.

A distinguished service award for his work in medicine was awarded to Dr. Guy E. VanDemark, Sioux Falls. Dr. VanDemark was the first doctor in the state to limit his work to orthopedic surgery, and the first to pass examinations of the American Board of Orthopedic Surgeons and become a diplomate of that board.

* * *

WORK began in July on the Donahoe Clinic, a new medical center in Sioux Falls. Dr. S. A. Donahoe and his son Robert Donahoe will practice general surgery; another son, John W. Donahoe will practice internal medicine and diagnosis; and Dr. Russell Orr will practice obstetrics and general medicine.

* * *

A MEDICAL RESEARCH TEAM, consisting of Arthur G. Steinberg, Ph. D., geneticist, Allen Richardson Jones, M. D., hematologist, and Mrs. Edith Steinberg, technician, were stationed at Sacred Heart Hospital during July and August to collect data on the blood groups of the three Hutterite colonies in the Yankton area. The Hutterite people were selected for the project—the object of which is to learn how heredity affects health and well-being—because they have large families with three or four generation living in a small geographic area, and because they keep excellent family records.

* * * *

THE Medical Officers Association of the Bureau of Indian Affairs was held at the Sherman Hotel, Aberdeen, on August 6 and 7. Sixty delegates from North and South Dakota and Nebraska attended.

* * * *

DR. L. L. PARK, Canton, was honored by the Canton Rotary Club for his 40 years of practice in the Canton Community.

Deaths . . .

DR. WILLIAM F. C. HEISE, 78, veteran Minnesota doctor and founder of the Heise clinic in Winona, died on May 29. His five sons, Doctors Herbert, William, Philip, Paul and Carl, still are associated with the clinic.

* * *

DR. HARRY W. CHRISTIANSON, 59, Minneapolis, died June 11. Dr. Christianson studied at the University of Minnesota, engaged in private practice at Wykoff from 1921 to 1929, served a fellowship at Mayo clinic from 1929 to 1932, and since 1932 had been in practice in Minneapolis.

Dr. John L. Crenshaw, 71, retired Mayo Clinic urologist, died June 17.

* * *

Dr. W. R. McCarthy, 67, St. Paul, died June 22 at Van Nuys, California. Dr. McCarthy practiced medicine in St. Paul from 1912 until he retired last winter. He was a past president of the Ramsey County Medical Society.

* * *

Dr. Alexander Aubin, 80, Minneapolis, died on June 27. Dr. Aubin retired in 1948, after practicing in Minneapolis for 36 years.

* * *

Dr. Linus F. Leitschuh, 41, Winsted, Minnesota, died on June 28. A graduate of the University of Minnesota medical school in 1939, Dr. Leitschuh had practiced at Red Lake Falls, Foley, Minneapolis and Winsted.

* * * *

Dr. F. P. Kortsch, 49, of Prior Lake, died July 15. He was a member of the Scott-Carver Medical Society, A.M.A., and was on the staffs of St. Barnabas Hospital in Minneapolis, Community Hospital at New Prague, and St. Francis Hospital in Shakopee.

* * * *

Dr. Joel C. Hultkrans, 59, a Minneapolis psychiatrist for thirty years, died July 27. Dr. Hultkrans was a member of Central Neuropsychiatric Association, American Psychiatric Association, Minnesota Society of Neurology and Psychiatry, and national, state, and county medical associations.

* * * *

Dr. Alfred E. Borgen, St. Paul, Minnesota, was drowned in a boating accident on August 8. A graduate of the University of Minnesota Medical School, he had taken his internship at St. Mary's Hospital in Duluth.

Dr. Gottfried Schmidt, 82, was killed August 6, when struck by a freight train near his home in St. Paul Park. A graduate of the University of Minnesota Medical School, Dr. Schmidt practiced 40 years in Sleepy Eye and Lake City.

* * * *

Dr. Joseph P. Flynn, 79, Minneapolis, died August 21. Dr. Flynn had practiced medicine in Minneapolis 49 years.

A.C.H.A. News

The Fourth National Conference on Health in Colleges will be held May 5-8, 1954 in the Hotel Statler, New York, N. Y. The Conference objectives will be: (1) To consider ways for protecting and improving the health of college students through comprehensive and integrated programs of health service and health education; (2) to formulate suggestions for relating college health programs to all other college functions. Participants will include college administrators, deans, directors of student health services, physicians, nurses, health educators, physical educators, and students. Dr. J. L. Morrill, President of the University of Minnesota, is serving as President of the Conference. Members of the Executive Committee are as follows:

Dana L. Farnsworth, M.D., Chairman; Charlotte V. Leach, Secretary; P. Roy Brammell, Ph.D.; E. Muriel Farr, R.N.; Charles C. Wilson, M.D.; Carl R. Wise, M.D.; Chairman, Committee on Local Arrangements; Dorothy B. Ferebee, M.D.; H. F. Kilander, Ph.D.; S. S. Lifson; Norman S. Moore, M.D.; George F. Anderson, Ed.D.

The Journal Lancet

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

Surgical Injuries of the Ureters*

CHARLES D. CREEVY, M.D.

Minneapolis, Minnesota

URETERAL INJURIES occur most frequently during operations upon the female genitalia or the lower large intestine, usually in the presence of dense adhesions, infiltrating neoplasms, brisk bleeding which is hard to control, and excessive stripping of the ureter. They may also be damaged during operations upon the pelvic floor. The urologist has occasion to cut deliberately and reimplant them during removal of diverticula and cancers of the bladder, and in the correction of retrocaval ureters and ureteral strictures. He may also overdo stripping of the ureter during ureterosigmoidostomy.

TYPES OF INJURIES AND DIAGNOSIS

A number of types of injury may occur. The intact ureter may be pinched off when sharply angulated by adjacent ligatures or sutures; it may be perforated by stick ties, or divided with or without ligature or removal of a segment; a piece may be snipped off laterally; or it may undergo rapid or gradual necrosis following crushing by a clamp or destruction of its extrinsic blood supply following energetic removal of part of its adventitia in an effort to excise all of the adjacent lymphatic tissue during an operation for cancer.

The nature of the resulting symptoms depends upon whether the injury is unilateral or bilateral, whether occlusion is complete or incomplete, and whether the injury results in leakage of urine to the peritoneal cavity or to the outside.

Complete bilateral occlusion usually causes anuria without other manifestations until uremia develops. Fever may occur if the ureter of an infected kidney is ligated. Unilateral complete obstruction is ordinarily entirely silent except in the presence of an antecedent renal infection, in which case chills, fever, renal pain, and toxemia may develop, but these phenomena are more likely to follow partial obstruction. The volume of the urinary output is not altered by unilateral injuries.

If the damaged ureter leaks into the peritoneal cavity, signs of free intraperitoneal fluid and of peritoneal irritation will be added to the symptoms already mentioned; uremia follows bilateral leakage. Retroperitoneal extravasation may produce signs suggestive of a perirenal or psoas abscess. Escape of urine from the abdominal or vaginal wound means, of course, that there is an ureteral fistula. It may be differentiated quite readily from a vesical fistula by distending the bladder with colored fluid (indigo carmine). If the dye escapes from the fistula, the urine is leaking from the bladder rather than from the ureter. It is true that this may occur from an ureteral fistula when there is reflux of urine up the ureter from the bladder, but this is uncommon in the female; its occurrence may be verified by cystography.

CHARLES D. CREEVY *was graduated from the University of Minnesota in* 1927, *serves as professor of urology and chief of the division of urology at the University of Minnesota hospitals.*

*From the Division of Urology in the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota. Presented before the regional meeting of the American College of Surgeons in Minneapolis on March 25, 1952.

Cystoscopy is indicated whenever any of the above symptoms or findings follow operations in the vicinity of the ureters. Excretory urography is likely to be unsatisfactory because of the presence in the bowel of excessive amounts of gas, and because the presence of a fresh wound makes impossible the satisfactory application of the abdominal compression so necessary for a good urogram. After inspection of the bladder to make sure that it is intact, the ureters are catheterized. If catheters pass readily to both renal pelves and recover clear urine, one has, for practical purposes, excluded any ureteral injury except a small perforation; if there is reason to suspect that one is present, it is wiser to leave the catheter in the affected ureter than to try to verify the presence of an ureteral fistula by ureterography, lest it be impossible to reinsert the catheter into the damaged ureter. If the inlying ureteral catheter is well placed with its eye in the renal pelvis, and is carefully secured in position, the fistula will probably heal.

The same thing is true if a catheter can be passed to the renal pelvis from the ureteral orifice despite the presence of an ureterovaginal fistula; if the catheter is left in place, the fistula may heal spontaneously or after light electrocoagulation of its vaginal opening.

If there is any evidence of leakage of urine into the peritoneum or behind it, free drainage must be supplied. If the catheters pass full length but no urine can be aspirated, one must suspect that the ureters have been divided so that the catheters have passed out of the ureters at the site of injury. This is easily verified or disproved by injecting a little contrast medium into the catheters and exposing a film. If the injected agent is outside the urinary tract, immediate repair is indicated; it will be discussed later. If normal renal pelves are outlined, ureterograms should be made to exclude the presence of perforation (figure 1).

Most often it will be impossible to pass a catheter beyond the site of injury, a finding which demands immediate operation if the obstruction is bilateral. Unilateral lesions should be operated upon promptly, but are emergencies only if there is evidence of intra- or retroperitoneal leakage, since Hinman has shown that the kidney of the dog may recover, in favorable circumstances, after complete ureteral occlusion lasting as long as three weeks. One should remember, however, that the presence of infection in the blocked kidney demands prompt action if the organ is to be saved without undue risk to the patient, and that waiting too long in the hope that an occluding or kinking ligature will be absorbed may lead to so much fibrosis at the site of injury as to make repair difficult. There is no great hurry when ureterovaginal fistula is the only sign of injury.

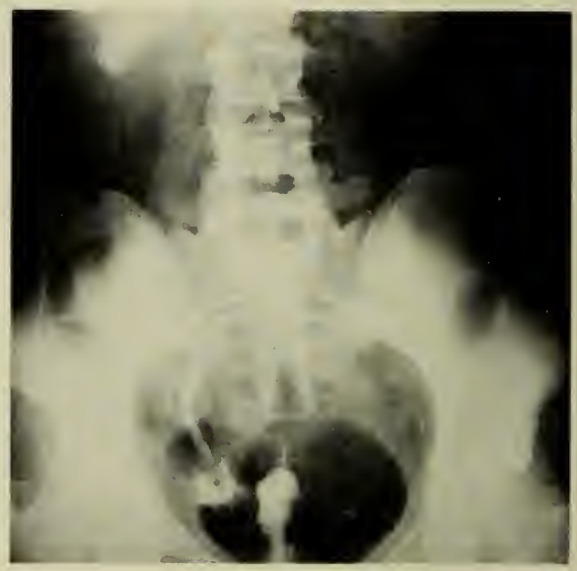

Fig. 1. Ureterovaginal fistula.

TREATMENT

The best course to follow in the presence of bilateral complete obstruction of the ureters depends upon the general condition of the patient. If it is poor, the safest course is to make a unilateral nephrostomy; as soon as the general state is satisfactory, the abdominal wound should be reopened (or an abdominal incision made if the original operation was a vaginal one). In patients in good condition the abdomen is opened at once. The ureters above the site of obstruction are dilated and can be followed quite readily to the point of injury. Urinary leakage can be seen. Ligatures and sutures from the point of injury downward are removed until any kinks or constrictions disappear. If no urine is seen outside the ureter, one may puncture it above the level of the former obstruction with a fine needle and inject a solution of methylene blue or indigo carmine. If none leaks out of the ureter, and if it can then be recovered from a catheter previously placed in the bladder, ureteral continuity has been reestablished and it is safe to close the abdomen with drainage. In the case of bilateral injury of this type, it is desirable to use indigo carmine for the first side and, after it has been re-

covered from the bladder, to inject phenolsulphonephthalein on the other side. The fluid recovered from the bladder is then made alkaline to decolorize the blue dye and bring out the red of the phenolsulphonephthalein.

A small lateral wound of the ureter may be sutured with fine (0000) chromic catgut in the adventitia, and the above mentioned test repeated. If the result is satisfactory, abdominal closure with extraperitoneal drainage may be made. If there is a large laceration or complete division of the ureter, one should pass a small catheter down the distal segment into the bladder to make sure of its patency. It is then withdrawn, and a small perforation is then made in the distal segment of the ureter below the injury. The largest Robinson (two-eyed) or polyvinyl catheter that fits snugly into the ureter without distending it is then passed up through the site of injury into the renal pelvis and secured to the adventitia of the ureter at the point of entry with fine chromic catgut. The flared end of the catheter is brought out extraperitoneally, and the abdomen closed with drainage. If the distal segment cannot be found, one may sometimes locate it readily by inserting an ureteral catheter into it through a cystoscope. If this fails, a tubed flap of bladder may be used to replace the lost segment. This will be discussed later.

The type of repair to be employed if the ureter has been severed depends upon the condition of the ureter itself. If it has been divided cleanly without crushing, and if its lumen is larger than normal, a catheter is threaded up to the renal pelvis as described above, and a simple end to end anastomosis is made over the catheter with four or five loosely tied sutures of 0000 or 00000 chromic catgut in the adventitia (figure 2), any crushed tissue at the severed ends being trimmed off first.

If the lumen is small, a stricture is likely to follow this type of repair, and an oblique or terminolateral anastomosis (figure 2) is to be preferred because they make the circumference of the suture line much larger so that, in the absence of an unusual amount of postoperative scarring, a good lumen at the anastomosis will result after contraction of the scar is complete. The sleeve type of anastomosis found in all the textbooks, in which the upper end of the ureter is invaginated into the lower end, is objectionable because it leaves a ledge within the ureter; this may defeat all attempts to dilate the ureter postoperatively should this become necessary,

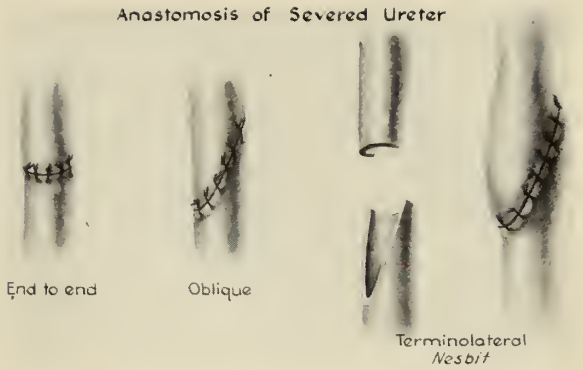

Fig. 2. See text.

and necessitate reoperation or even removal of the kidney.

When a segment of the ureter is missing, the location as well as the length of the defect becomes important. Short defects may be overcome by mobilizing the ureter with some of the surrounding tissues above and below the defect, taking care to preserve as much of the extrinsic blood supply as possible, and making one of the anastomoses already described. If the segment missing is above the brim of the true pelvis and is too long for anastomosis, it may be wise to implant the upper segment into the sigmoid (figure 3). McArthur has successfully bridged a defect too long for a direct union by passing a catheter from the bladder or from a perforation in the distal segment up to the renal pelvis, suturing the soft tissues loosely around the exposed portion of the catheter, and leaving it to Nature or to Providence to rebuild the missing segment. He made no followup studies of the kidney. This has always seemed to me to be demanding too much of Mother Nature.

Higgins, Moore, and Smith have each reported success from mobilizing the upper segment of

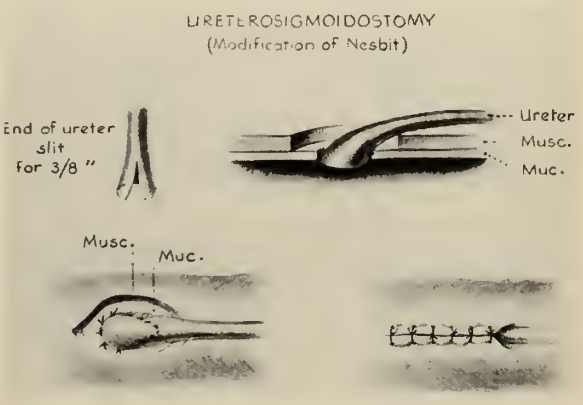

Fig. 3. Mucosa to mucosa anastomosis of ureter to sigmoid plus closure of muscularis.

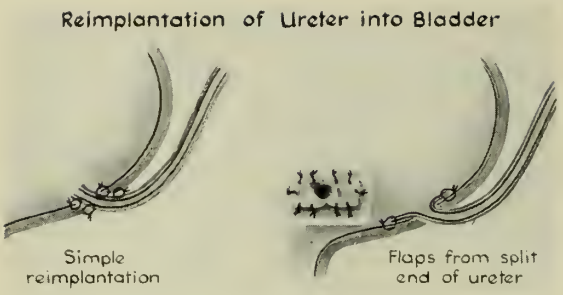

Fig. 4. Same kidney as in figure 3 but one year after ureterosigmoidostomy.

the damaged ureter, drawing it beneath the posterior parietal peritoneum, and anastomosing its end to the side of the intact opposite ureter. This seems to me to be justifiable only if the opposite kidney is damaged, because otherwise one endangers the sound kidney for the benefit of the injured one if anything goes wrong; a stricture at the anastomosis cannot be dilated.

When the defect is in the pelvic ureter, the upper segment may be mobilized and reimplanted into (figure 4) or anastomosed to the bladder (figures 5 and 6) particularly if the missing segment is short or if the upper segment of the ureter is dilated, and therefore elongated. If it is found that the injured or missing portion of the ureter is so long that neither reimplantation nor anastomosis is possible without tension, one may fashion a flap from the wall of the bladder (figures 7 and 8), convert it into a tube, and implant the ureter into it or make an anastomosis between them. If the bladder is normal in size a considerable length of pelvic ureter can be replaced in this manner, but if the bladder is fibrous and contracted, this cannot be done, and ureterosigmoidostomy may be considered.

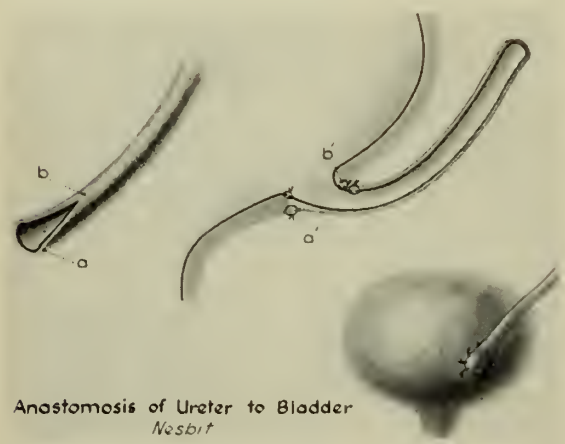

Fig. 5. See text.

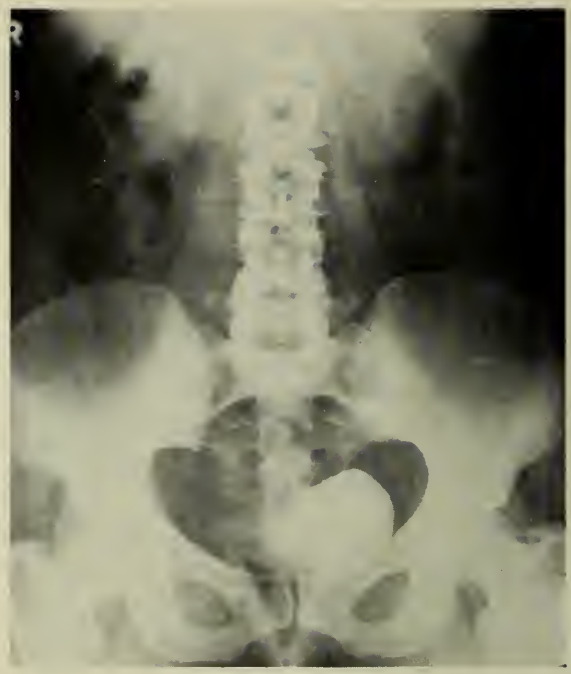

Fig. 6. Urogram 15 years after division and reimplantation of right ureter.

These techniques are applicable to all types of surgical injuries of the ureters, including those discovered at the time of the original operation, those found within a few days, and those which manifest themselves after an interval, as is often the case with ureterovaginal fistula.

GENERAL PRINCIPLES OF URETERAL REPAIR

Certain general principles are common to all operations for repair of the ureter. Nonabsorbable sutures should never be used in the urinary

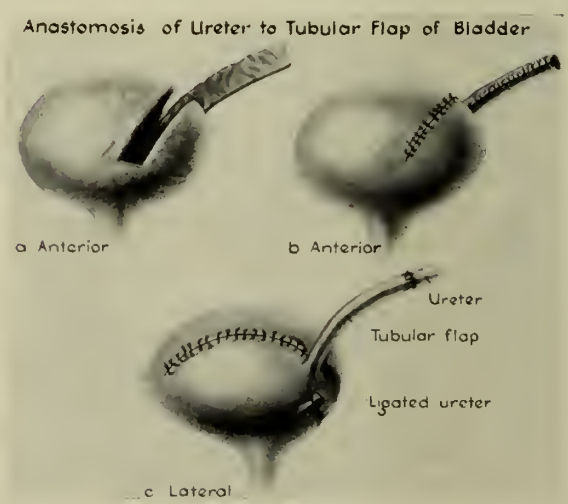

Fig. 7. See text.

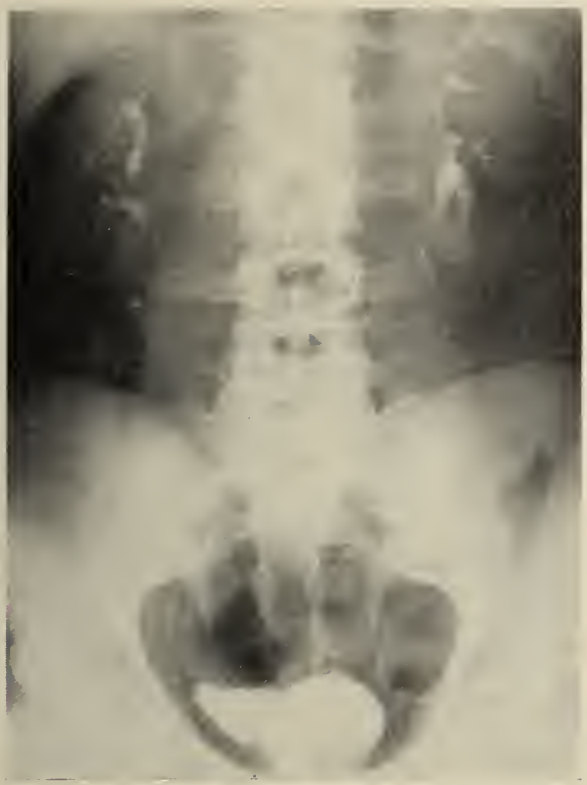

Fig. 8. One year after anastomosis of right ureter to tubular flap of bladder.

tract itself, not even in its adventitia, because they will almost inevitably work their way into the lumen of the urinary tract, there to become incrusted with urinary salts. There should be no tension whatever at the site of repair. All sutures should be loosely tied, aiming at approximation without necrosis. The urine should be diverted from the area of any extensive repair of the ureter by means of nephrostomy, pyelostomy, or ureterostomy, or conducted past it by means of a catheter. The latter is usually simpler and is preferred because the inlying catheter keeps the repaired ureter straight, and separates granulating surfaces during healing so that they cannot become adherent. One may pass one end of the catheter down into the bladder and the other up to the kidney, fishing the distal end out through the urethra or through a puncture in the anterior wall of the bladder. However, it is easier to bring the distal end of the catheter out of a puncture in the wall of the ureter below the injury; moreover suturing the catheter to the ureteral wall at the site of its emergence is effective in keeping it from slipping down before the time for its removal. All such catheters should be left in place for from fourteen to twenty-one days, depending upon the smoothness of the convalescence. Drains alongside these catheters may be removed as soon as drainage around them ceases to do more than stain the dressing.

T tubes may be used to pass urine through an anastomosis or repair, but I am always uneasy after using them because the upper arm of the T does not reach the renal pelvis; this increases the possibility that urine may pass around the tube and damage the repair.

It is wise to administer an antibiotic or urinary antiseptic while catheters are in place. This will not prevent infection, but will serve to minimize it. One may start, during the immediate postoperative period while the patient is unable to take oral medication, with streptomycin and penicillin. This may be replaced within a few days with oral sulfadiazine or Gantrisin in moderate doses. Aureomycin, terramycin, and Chloromycetin are reserved, because of their cost and because of the irritative effects of the first two when administered for long periods, for short term treatment or for serious infections.

The fluid intake should be high while a catheter is in place primarily to flush the catheter and so to reduce the danger of plugging. The chief danger of an inlying catheter used for long periods lies in the introduction of urea-splitting bacteria into the urinary tract with resultant encrustation of the tubes and the later formation of stones. For this reason it is probably wise to administer Basaljel while the catheter is in place, thus keeping much of the dietary phosphorus in the bowel and reducing the excretion in the urine of phosphates, an important constituent of the encrustations. Early and frequent ambulation are important in preventing stasis of the urine in the dependent calices of the kidney, another important factor in the formation of stones.

If both ureters have been completely obstructed for some time before repair, one must remember that the ensuing diuresis may result in the loss of a good deal of salt and water from the body, and should adjust their intake accordingly.

Late followup after a successful repair of ureteral injury is as important as a successful operation to make certain that neither stricture, secondary infection, nor lithiasis ruin the result. This means that the urine must be sterilized after healing has occurred, and that periodic excretory urograms or retrograde pyelograms should be made until danger of stricture is past — usually a matter of a year or two. If narrowing of the anastomosis or hydronephrosis above it appear, ureteral dilatation is required.

NEPHRECTOMY AND URETERAL LIGATION

It will be noticed that I have not mentioned deliberate ligation of the injured ureter nor nephrectomy as satisfactory methods of treatment. Both are objectionable unless preoperative studies of the patient have shown unmistakably that the opposite kidney is capable of supporting life alone. This implies at least a good excretory urogram capably interpreted. Palpation of the opposite kidney at operation is a very poor guide to its functional capacity, and should be relied upon only in a grave emergency, since badly damaged kidneys may feel quite normal, even to the experienced urologist. In case of doubt it is far more conservative to make a temporary nephrostomy, pyelostomy or even a cutaneous ureterostomy and to swallow one's pride. Ureteral ligation has certain disadvantages of its own: it may lead to a fulminating acute pyelonephritis if the kidney is infected; the ureteral ligature, no matter how carefully placed, may slip or cut through. Therefore, ureteral ligation has no place in the treatment of ureteral injury except in dire emergencies.

The prophylaxis of ureteral injury is largely a matter of care in dissection and of the exercise of foresight. One should remember that the ureter may be displaced by neoplasms or inflammation; it may be pulled up with the peritoneum. Rough, hasty, slashing dissection should be avoided; one must never grab blindly for a bleeder in a pool of blood in the region of the ureter. If a difficult dissection is anticipated, it is cheap insurance to insert a large catheter into each ureter just before operation; this can be done while the abdomen is open if unexpected difficulties are encountered, even by a relatively inexperienced cystoscopist.

SUMMARY AND CONCLUSIONS

1. Surgical injuries of the ureters occur most frequently during difficult or bloody pelvic dissections.
2. Their recognition is usually simple.
3. The principles of their repair are discussed.

Urologic Pain

PAIN from urologic conditions is usually experienced at sites distant from the actual lesion, and affords striking examples of referred or reflected pain. One of two characteristic types of pain is usually present, either a dull almost continuous ache, or sharp colicky pain, often radiating, in the costovertebral angle. Pain in the costovertebral angle and radiating anteriorly requires careful attention to the kidney, even in the absence of positive findings from urinalysis and urologic studies.

Dull backache results from pulling and stretching of the renal capsule, is felt at the costovertebral angle, and is confined to a circular 8 to 10 cm. area, with an occasional radiation impulse to the abdomen anteriorly. Renal and ureteral pains are closely related and frequently due to demonstrable calculi, although in many cases calculi cannot be demonstrated roentgenographically, even in the presence of hematuria.

Obstructive ureteral distension first affects the renal pelvis and then the capsule, and is the basis of renal colic of ureteral origin. Associated spasm may exist alone or be secondary to intraureteral detritus, blood clot or calculi; mural lesions such as primary carcinoma, ureteritis, stricture, polyps, or ureterovesical cysts; or kinks or angulation of the ureter from bands or aberrant vessels, ureteral adhesions, and from pressure against the ureter.

The knife-like intermittent pain of ureteral colic may be centered anywhere between flank and groin, with or without radiation to the testis, or labium, or anterior thigh. Pain from upper ureteral involvement is frequent in the corresponding flank.

Ureteral lesions near the bladder cause pain on defecation, urination and ejaculation. Obstruction of the intramural ureter produces frequency and urgency referable to the bladder, and also dysuria. Intravesical lesions produce the more severe and constant pains in the bladder.

J. ULLMAN REAVES: Evaluation of urologic pain. J. Int. Coll. Surgeons 18:566-570, 1952.

ACTH and Cortisone in Allergy*

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ALLERGY, in its real implications, is a term used to designate the abnormal altered tissue response of certain people to the stimuli of their environment whether these be physical, chemical or pyschic.[1] It is the abnormal reaction of their cells to the world about them. From this point of view it is evident that a great many conditions that we ordinarily do not think of as allergic could be included in that category. It is also evident that certainly to the laity and almost as certainly to the medical profession, the term "allergy" is restricted to that group of altered reactivity diseases that have a marked hereditary tendency, hypercontractivity of smooth muscle, immediate whealing skin reactions or flaring, production of specific antibodies or reagins, and symptoms of vasomotor origin. It has become increasingly clear in recent years that even in these restricted conditions commonly regarded as allergic where hypersensitivity may play a very striking role, it is the pattern of tissue response that is fundamentally important. The manifestations may be initiated by a wide variety of stresses and stimuli.[2] In the words of Selye "the abnormal adaptive response of the agent is the major cause of the disease."[3] With the development and use of ACTH and cortisone came the hope that these hormones might favorably alter this fundamental, unfavorable biologic response of the allergic person.

Before assaying the role of ACTH and cortisone in the management of allergic problems, a brief resume of our present concepts and orthodox methods of treatment would be indicated. A hypothesis in science, certainly in medicine, need not be 100 per cent correct to be of great help, especially in the field of therapeutics.

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In the allergic individual, we first must have the so-called allergic state – a condition often inherited in which the patient is more likely to develop the symptoms of allergy than do others in exactly the same environment. It is the soil in which allergy in the usual sense can flourish.[4]

TABLE 1

Allergic state + exposure to an allergen or stimulant = sensitized state
Sensitized state + allergen = antibody production
Antibody + allergen = toxic product
Toxic product = symptoms

We have further the capacity in these people to become sensitized so that upon re-exposure to an allergen they respond with the production of antibodies. The union of the antigen and antibody results in the release of a toxic agent – histamine or histamine-like – which in these patients causes a variety of symptoms of vasomotor origin.[5]

Treatment of allergics, irrespective of the shock organ involved, is based on an accurate diagnosis of a true hypersensitive state and interference with these various hypothetical processes going on in the allergic individual. Everything that itches, wheeezes or sneezes is not allergy, not even in the allergic. The ideal approach would, of course, be an attack on the fundamental asthmatic state but unfortunately in allergy, we know as little about that fundamental factor as does the cardiologist about coronary disease, the psychiatrist about mental disorders or the gastroenterologist about cirrhosis of the liver. We do not know why the guinea pig is easily sensitized while the rat is very resistant. The next method of approach would be prophylaxis of the asthmatic state. While heredity is important in allergy, eugenics is very hard to put in practice and is of very little actual help. A more practical method is to tell people with a background of that type to avoid commonly known sensitizing agents such as pollens, fungi,

*Read before the general staff meeting of the University of Minnesota Hospitals, February 27, 1953.

animals, dust, antigenic injections, and prolonged emotional and physical trauma.

The third method is avoidance of the causative allergens or stimuli which, of course, implies recognition of these etiologic factors by history, physical examination, laboratory procedures, skin tests, and therapeutic trials—the most important being history. This may be accomplished by removal of the patient from the allergens, placing a barrier between the patient and allergen, or removal of the allergen from the patient.

The next method of treatment is by modifying the antibody formation or the allergen-antibody reaction. While nitrogen mustard, x-ray and isotopes[6] have been tried to modify the antibody response, these methods are dangerous and at present, impractical. The most successful therapy at this level has, of course, been by specific hyposensitization. This method apparently acts by production of blocking or thermostable antibodies which interfere with the union of the antigen and the thermolabile antibody on the shock tissue cell.[7] Another theory is that these injected specific antigens stimulate the alarm mechanism with resulting amelioration of symptoms due to ACTH.[3]

The next method of approach in this theoretical concept is to neutralize the histamine or histamine-like substance resulting from the union of antigen and antibody. While, as pointed out by Dragstedt,[8] histamine release is at least a major factor in the causation of allergic symptoms, it is probably not the only factor. It is because of this that Sir Thomas Lewis[9] called the factor "H substance" and said "I shall speak of an H substance and in using it shall mean any substance or substances liberated by the tissue cells which exert on the minute vessels and nerve endings an influence culminating in the 'triple response.'" While the histamine theory is plausible, the antihistamines, as reported here in 1949, although of a great deal of help in some minor allergic disorders, have proven of very little practical help in the more severe complicated conditions and in particular, asthma.

TABLE 2

Allergen + antibody = toxic substance system = antibodies
Allergen + antibody = toxic substance
Toxic substance → hypophyses = ACTH
ACTH → adrenals = cortisone and DOCA

The last method of treatment is symptomatic. These are too numerous to mention and include the parasympathetic depressants, the sympathetic stimulants, the iodides, anti-bariums, etc.

As, by very definition, allergic diseases are diseases of adaptation, resulting from man's reaction to his surroundings. Selye's[3] concept of the general adaptation syndrome, whether entirely correct or not,[11] is of a great deal of help especially in evaluation of the role of ACTH and cortisone.

The antigen stimulates the reticuloendothelia system especially the plasma cells to produce antibodies. The resulting toxic agent resulting from the reaction of the antigen and antibody, according to Selye, directly or indirectly stimulates the hypophysis to produce ACTH. ACTH in turn stimulates the adrenals to produce cortisone and DOCA. If the response is too violent or the gluco-corticoids are inadequate, allergic reactions result. As the glucocorticoids mitigate the response of the shock tissues to stimuli and the mineralo-corticoids increase the responsiveness, the degree of sensitivity would depend on the balance between these two hormones.

As I pointed out in a report on the use of ACTH and cortisone in asthma in 1951,[12,13] it was immediately evident from the effects of ACTH and cortisone, that they would have profound effects in the sensitivity states. This was confirmed before and since then by many reports, especially on acute symptoms and for relatively short periods of time.[14,15–20] Whether as pointed out by White[21] and Sayers,[22] these hormones act by (1) interference with release of or the toxic action of anaphylactagenic substances produced in the antigen-antibody reaction, (2) alteration in the relative concentration of antigen and antibody in the tissues or factors which influence the combination, (3) alteration in cell permeability through action on hyaluronidase, or (4) alteration in tissue response to the antigen-antibody reaction; it is very evident that early in the course of treatment of allergic individuals with ACTH and cortisone, there are changes of induced hyperactivity of the adrenal cortex. These need not be here re-enumerated. In evaluation of the effect on chronic severe allergic cases here reported, however, we must also and especially consider the euphoria induced, the increased appetite and neuropsychiatric changes.

As would be deduced from the effects and confirmed by the literature,[23] absolute contraindications to the use of ACTH and cortisone are few but they should be used with caution in diabetes mellitus, psychotic disorders or emotional instability, cardiac failure, during major

surgery, severe infections, myocardial infarction, pulmonary embolus, cerebral accidents, osteoporosis, tuberculosis, syphilis and peptic ulcers.[12,13] Very important is the question of the effects of long continued administration and large dosage. In general, the response is neither rapid nor long continued. The effects are reversible when the hormone is discontinued. And it is indeed encouraging to know that in Cushing's disease, due to a unilateral tumor of the adrenal cortex, the other adrenal cortex may undergo atrophy, but its function returns even years later after the tumor is removed. Beyond that, it is neither necessary nor desirable to give large doses for a prolonged period.[24] The immediate undesirable clinical effects reported are edema and hypertension, masking of symptoms and signs of infection, decreased localization of infectious processes, diabetogenesis, perforation of gastrointestinal ulcerations, precipitation of psychosis, muscle weakness, osteoporosis, hirsutism, loss of head hair, acne, pigmentation, Cushing's syndrome, impaired wound healing, and increased coagulability. The effects are probably due to the undesirable metabolic effects of protein catabolism, $Na+$ and water retention, K^+ loss, derangement of carbohydrate metabolism, Ca and PO_4^{---} depletion and depletion of other essential constituents of protoplasm.[25,26] The effects are usually not marked certainly in the dosage used in allergy and are easily controlled by discontinuance or reduction of the amounts prescribed. Sodium limitation, especially in patients receiving in excess of 10 mg. of ACTH or 50 mg. of cortisone daily, is indicated, while in many receiving large dosage, restriction to less than 300 mg. daily may be necessary. A high protein diet of 120 to 200 gm. daily with adequate calories and high in potassium is logically advised especially in undernourished individuals.[27] Very infrequently diuretics may be indicated. While the weakness noted at times has no constant relation to low serum levels or resulting EKG changes, it has at times been desirable to give potassium chloride especially when the level is below normal or when the hormones are to be given in large doses or a prolonged period of time. Estrone and progesterone or testosterone will frequently prevent the most annoying of the symptomatic side effects in menopausal women where they are most frequent. Above all, suboptimal dosage at the lowest possible level will minimize these undesirable features in the use of ACTH and cortisone.[12]

In the present state of knowledge and expense, these hormones should be used in allergies only where the diagnosis is well established and where the other means of therapy already reviewed do not adequately control the disease. It is by now certainly evident that ACTH and cortisone, whatever the mode of action, are blocking agents and have no specific effect. Beyond that before starting therapy the relative expense, hazards and contraindications must be taken into account not only in short term but also in the probably necessary long term use of these agents.

With all these thoughts in mind and to minimize the dangers involved, the following procedures in table 3 were carried out in all patients before therapy was started.

TABLE 3
BEFORE THERAPY

1. Routine urinalysis
2. Blood, Hgb., Wbc., differential
3. Erythrocyte sedimentation rate
4. Blood N.P.N. or urea when indicated
5. ECG if indicated especially when over age 45
6. Thorn test with ACTH
7. Weight
8. Blood pressure
9. X-ray

During therapy the procedures in table 4 were done.

TABLE 4
DURING THERAPY

1. Urinalysis (at least weekly)
2. Blood sugar estimation (if patient is glycosuric)
3. Glucose tolerance test (if patient is hyperglycemic)
4. Erythrocyte sedimentation rate at weekly intervals (optional)
5. EKG to detect K depletion
6. Blood pressure
7. Weight

As I reported in 1951[13] when cortisone became more available and less expensive, the opportunity presented itself to give this hormone to ambulatory patients with severe, chronic, perennial asthma. All the usual specific and non-specific measures had been tried with little or no or very temporary effect and a progressively downward course in these semi-invalid or invalid people. The initial dose was 200 mg. (100 mg. intramuscularly in each buttock). Thereafter the dosage was 100 mg. daily for six days. In the second and third week the dosage was reduced to 100 mg. three times a week. Here we discontinued treatment to see if we could get a remission. If none was obtained or if symptoms recurred gradually, treatment was again started. The dosage depended upon the response of the indi-

vidual patient. No attempt was made to have the patient completely free of symptoms as long as he was comfortable. After obtaining a satisfactory effect, cortisone was given by mouth in equivalent dosage and with apparently approximately equivalent results. Cortisone acetate in the same form supplied for injection was mixed in milk or fruit juice until the drug was available in tablet form. As the effects of the orally given hormone is dissipated in 12 to 14 hours, it was prescribed in two or three divided doses.

TABLE 5

Number of patients	30
Ages	15 to 62
Males	22
Females	8
Duration of asthma	3 to 32 years
Diabetics	2

Thirty patients with allergic asthma chosen for their extreme severity, chronicity and failure on the normal allergic regime were given cortisone in the manner described and under the above precautions and conditions. No patients with usual contraindications were treated but for 2 asthmatics with mild diabetes mellitus. The ages varied from 15 to 62. Twenty-two were men and 8, women. The duration of the disease varied from 3 to 32 years. The apparent causation of the allergy ran the gamut of allergens. Psychic factors were present as in all asthmatics to a greater or less degree.

TABLE 6
RESULTS

Good	22
Fair	8
Poor	0

The initial results in these cases, as I reported, were to me in the beginning really startling. Within a day to a week there was a marked diminution in wheezing with a feeling of well-being and energy. The cough lessened and in many cases almost disappeared by the second or third week. As the dosage was decreased, the euphoria and enthusiasm was decreased but the over-all result was still very satisfactory. Results were evaluated according to the patient's own description and judgment and the over-all picture including objective findings. Those who experienced 50 per cent relief or more were considered to have fair results. Patients with mild or practically no symptoms were considered to have good results. By this criteria the initial results of treatment were good in 22 and fair in 8. In the 8 that had only fair results there was more or less persistent cough but no frank severe asthmatic attacks — a real achievement in this type of case.

TABLE 7
SIDE EFFECTS

Increased appetite	24
Euphoria	18
Acne	1
Edema (transient)	3
Glycosuria	2
Furunculosis	1
Change of shock tissue	1

The early side effects in this series of patients were not many and not serious. Increased appetite was noted in 24 though this had a tendency to decrease with decrease in dosage. Euphoria, mild and quite pleasant, was noted in 18. This also decreased after the first few weeks. Severe acne was noted in 1 which was controlled by penicillin. Transient edema was mild to moderate in 3, but no medication was required beyond a reduction in sodium intake with a later reduction in the dose of cortisone. The only cases of glycosuria were in the 2 diabetics in whom insulin requirements were more than doubled during the first three weeks. When dosage was decreased, the insulin requirements returned to pretreatment levels. One case of furunculosis developed but subsided with use of penicillin. One case had a change of shock tissue and developed a severe urticaria which finally also responded to cortisone.

After four months treatment, one woman, age 44, developed emotional disturbances with a moderate degree of depression. One other woman, age 52, developed the same symptoms after three months of therapy. Cortisone was discontinued despite improvement in asthma of a marked degree in both. These two cases called attention to the reported possible mental effects of cortisone.[28] One male, age 38, developed a definite blurring of vision to the extent that here also therapy was interrupted though no objective findings were noted on ophthalmoscopic examination. This, to me, was of great interest in view of reported increased coagulability after cortisone and ACTH.[25,27] Knisely and Black[29,30] studied the peripheral circulation of the bulbar conjunctiva of human beings using reflected light and a binocular stereoscopic microscope. With similar technique Burrage[17] observed the vessels and circulating blood of the bulbar conjunctive of 6 patients before cortisone and at weekly intervals during therapy. He noted clumping of

TABLE 8
STATUS

Remission (with specific therapy)		8
Stopped therapy after asthma improvement		6
cannot afford it	3	
depression	2	
blurring of vision	1	
Improved on cortisone (plus specific therapy) (50 to 75 mg. daily)		2
Improved on intermittent course of cortisone		3
Improved with cortisone plus ACTH (gel) (plus specific therapy)		8
Relapse with ACTH plus cortisone plus specific therapy		3

cellular elements of the blood which never cleared during therapy and at times these clumps seemed to plug the ends of small arterioles intermittently.

An attempt was made at the end of three weeks to stop treatment to see if a remission could be obtained. If none occurred dosage was maintained to give adequate relief. The dosage varied from 12.5 mg. to 75 mg. daily and varied in different patients and in the same patient at different times.

At the end of two years of experience with oral cortisone the picture is not quite as impressive as it was at the beginning though still in the type of patient treated significant. In evaluating this result it is well to recall that many asthmatics have prolonged remissions for no apparent reason. I must also emphasize that more specific treatment was also searched for, instituted, or maintained at the same time. It also must be stressed, however, that these were desperate cases that had not previously responded at all to usual therapy.

We obtained a remission in 8 patients with no apparent relation to total dosage or duration of treatment. I wish to call particular attention to the 3 asthmatics who stopped treatment in spite of apparent improvement because they could not afford it. It is certainly no medical triumph to add a flat pocketbook to an unimproved asthma. The expense involved not only of the hormones that have and still are becoming less costly but of constant medical supervision must be explained before starting therapy. Two patients are satisfactorily controlled with 50 to 75 mg. of cortisone daily when other allergic measures are also adhered to. Three who could not afford continuous therapy and supervision and obtained more or less adequate remission for a period of three weeks to six months with a two to three week course of cortisone were given intermittent treatment with marked exacerbation of symptoms. Here, the usual procedure of initial large doses orally of 200 to 300 mg. in divided doses daily for two or three doses was given and then the dosage gradually reduced over a period of two to three weeks.

Eight patients did not get satisfactory improvement on the regime of cortisone alone and on maintenance doses of up to 75 mg. daily. Increased amounts gave grave side effects of increased hyper-adreno-corticism such as moon face, increased blood pressure, marked edema or increased weight in spite of the above mentioned precautions and procedures. In these 8, ACTH long acting (gel) form was given in addition to cortisone with the idea that by giving both cortisone and ACTH we might get the effect desired with smaller total dosage. We might also avoid the atrophy of the adrenals induced by cortisone or the hypertrophy of ACTH. While hypocorticoidism may normally be the most important stimulant for release of ACTH, it is not the only factor as ACTH production in stress is compatible with a high blood level of corticoids.[31]

Cortisone orally was maintained at 50 mg. daily. A dose of 40 to 60 mg. of ACTH gel intramuscularly was given the first day and daily doses thereafter in decreasing amounts until a satisfactory maintenance dose was attained. The dosage of both were varied to obtain the best clinical effect with the smallest possible total amount. This varied in different patients and in the same patient at different times from 50 mg. of cortisone plus 10 mg. of ACTH daily to 12.5 mg. of cortisone daily and 5 mg. of ACTH every other day. The patients were taught to give their own injections as are diabetics in giving insulin. Attempts to stop this treatment were made at intervals but to the present with no success in these patients. The dosage is constantly varied with the clinical state. While it is difficult to determine definitely that the smaller dosage of the hormones are specifically beneficial, prolonging periods between therapy resulted in gradual exacerbation of symptoms. Further attempts to discontinue cortisone resulted in exacerbation of symptoms unless ACTH was increased in disproportionately higher dosage.

HAY FEVER

Because of the usually dramatic but usually short duration and purely blocking effects of cortisone in allergic manifestations, it was long felt, as I intimated in my first report in 1951,[13] that a self-limited allergy would respond ideally to cortisone. As the symptoms of hay fever are usually limited to the duration of the pollinating season, after which the antigen is apparently no

longer active, the use of the hormone could also be used for a short period of time. Haddon Carryer[32] initially treated 3 patients with hay fever and asthma with cortisone and reported relief of the symptoms of hay fever though less rapid than those of the asthma. Gelfand[33] treated 2 patients with severe ragweed hay fever with 50 mg. of cortisone on the days of high pollen counts with marked improvement in symptoms. Schwartz and co-workers[34] report on the treatment of 25 patients with ragweed pollenosis with hyposensitization and added oral cortisone with good results in 21. Hyposensitization was continued due to the feeling that it was a more specific and safe method of treatment and had more lasting benefit especially as regards asthma. Others have reported on the effects of ACTH and cortisone in hay fever.[35,36] As pointed out by McCombs[37] "exactly what place pollen hyposensitization will have in the management of seasonal bronchial asthma when hormone therapy has been thoroughly evaluated cannot be ascertained as yet." While a great majority of patients obtain very satisfactory results at present, by pre-seasonal or perennial specific injection therapy, the considerable number that do not should logically be given a trial on hormone therapy.

A total of 36 patients with severe ragweed hay fever were treated under the same restrictions as the cases of asthma with same indications, contraindications and precautions. The ages varied from 18 to 56; 12 males and 24 females; the period of previous hyposensitization varied from two to fifteen years and the duration of symptoms from two to thirty years. In spite of previous treatments with varying degree of relief especially of the asthma, these people still had marked difficulty in spite of all available means. With start of symptoms, cortisone therapy was begun with 50 mg. orally four times a day for one day, then 25 mg. four times a day until relief was obtained. The dosage was then gradually reduced to a maintenance dose of 12.5 to 75 mg. daily, usually 50 to 75 mg. a day depending on degree of symptoms. No serious side effects were noted beyond occasional nausea, headache or abdominal fullness. Relief was obtained in one to ninety-six hours after treatment was started. Symptoms recurred in a brief period of a few hours to a few days with discontinuance of cortisone. Good results were obtained in 10, excellent results in 22. Four patients had no marked effect from the dosage used.

TABLE 9

ORAL CORTISONE WITH HYPOSENSITIZATION IN HAY FEVER

Number of patients	36
Ages	18 to 56
Males	12
Females	24
Previous treatment by hyposensitization	2 to 15 years
Duration of symptoms	2 to 30 years
Good results	10
Excellent results	22
Poor results	4

In 8 hay fever patients with definite pollen sensitivity by clinical history and skin tests, in a condition where correlation is usually excellent, reactivity as noted by scratch or intradermal skin tests persisted with no change even after prolonged treatment. The effect must be beyond the antigen antibody stage. This observation, confirming the results of Loveless and others[1,38,39] indicate, of course, that the fundamental therapeutic effect does not affect the mechanism of sensitization but may change temporarily the underlying pattern of tissue response. It emphasized also the need for continued study in these patients of the stimuli that call forth the abnormal response.

COMMENT AND SUMMARY

ACTH and cortisone in my opinion represent an important advance in the treatment of severe allergic states. While satisfactory symptomatic relief is almost the rule at the start, the real problem is maintenance of relief after the initial period with no serious effects. While I have kept 2 patients with severe asthma on cortisone and 8 asthmatics on cortisone and ACTH (gel) for two years almost continuously with no apparent serious effect, it must be emphasized that they have all been kept under constant and careful supervision with continuous attempts to stop medication or find a more specific therapy. Moreover, relatively small doses appear to be effective as compared with that required in most other serious conditions requiring hormone therapy.[33,36,37] Severe hay fever patients treated with cortisone in addition to hyposensitization had worthwhile relief under similar conditions and precautions.

In a disease so frustrating to patient and as frequently to the doctor as perennial, intractable asthma or even severe unrelieved hay fever with their devastating effect on social and economic life, even the reassurance that ACTH and cortisone will relieve the more acute episodes of the conditions is very comforting. Contrary, the letdown after cessation of treatment, if mandatory,

may be even more disappointing and devastating to some if no specific cause has been discovered meanwhile. By attention to more specific factors of usual allergic management coupled with the usual precautions, and on a regime of diet and medication as outlined, a considerable proportion of these unfortunates can be made more comfortable and returned to a useful place in society. Certainly, as pointed out by Kinsell,[27] the reaction of the profession to these hormones has swung from incredulity, to extreme euphoria, then to the extreme alarm reaction. With the phase of maturity and stability we must now recognize that while no substitute for usual allergic regime and with all the dangers involved, and they are very real, under proper care and precautions, with a true understanding of their lack of specificity in the field of allergy, at least many patients are now productively active who had been in a semi-invalid or fully invalid state before the use of ACTH and cortisone.

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Ilotycin (Erythromycin) for Fusospirochetal Infections of the Oro-Pharynx*

A Progress Report

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THE therapeutic efficacy of Ilotycin† (erythromycin) was tested in the treatment of 33 cases of fusospirochetal infections. The subjects were 33 healthy young men and women, college students between the ages of 17 and 24. Initial examinations and laboratory studies were conducted by our own personnel in the Out-Patient Clinic of Syracuse University, Syracuse, New York.

All 33 patients complained similarly of painful, bleeding gums — a condition that had continued from one day to three months. Acute inflammation and ulceration of the mucous membrane of the gingival margins was observed; in some cases the inflammation extended to the pharynx and buccal mucosa.

Smears of the bleeding and ulcerated areas were taken prior to treatment and examined for the presence of fusospirochetal organisms; this study includes only those patients whose smears were positive. In our laboratory a smear is considered positive if numerous fusiform bacilli and spirochetes appear often in association with numerous pus cells. A patient is considered bacteriologically cured when fusiform bacilli and spirochetes no longer appear in the smear and when pus cells are almost completely absent.

Ilotycin was used in capsules of two sizes, containing 100 and 200 milligrams respectively. These were administered in doses of either two capsules (400 mg.) four times daily, or two tablets (200 mg.) four times per day. Patients were observed every forty-eight hours. Average duration of treatment was forty-eight hours. In addition to Ilotycin, each patient was given orally from 600 to 800 mg. of vitamin C daily.

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RESULTS

Tables 1 and 2 present the results of this experiment.

TABLE 1
ILOTYCIN: 400 MG. FOUR TIMES PER DAY
(Total daily dose: 1.6 grams)

Total cases	24
Cases inadequately followed	5
Clinically cured	19
Bacteriologically cured	14

TABLE 2
ILOTYCIN: 200 MG. FOUR TIMES PER DAY
(Total daily dose: 0.8 grams)

Total cases	9
Cases inadequately followed	0
Cases clinically cured	6
Bacteriologically cured	4

Patients who received 1.6 grams of Ilotycin daily in divided doses exhibited prompt relief of pain and tenderness; gingival bleeding subsided within 24 to 48 hours. There was objective evidence of regression of inflammation and ulceration, and in the entire group receiving this dosage, in some areas the gingival tissues had returned to normal. When these patients were observed on the third and fourth days further regression of the disease was apparent; at the end of this time healing was nearly complete in all cases. Bacteriological sterilization of the mouth, on the basis of fusospirochetal content, did not keep pace with the clinical results; although healing had occurred in 100 per cent of the cases within the time specified, 27 per cent continued positive for fusospirochetal organisms.

Of the patients who received 0.8 grams of Ilotycin daily in divided dosage, six or 66 per cent, were clinically cured in accordance with the above criteria, and four, or 44 per cent, were bacteriologically cured.

*From the Department of Health and Preventive Medicine, Syracuse University, Syracuse, New York.
†Dr. J. W. Smith of Eli Lilly & Company generously provided the Ilotycin.

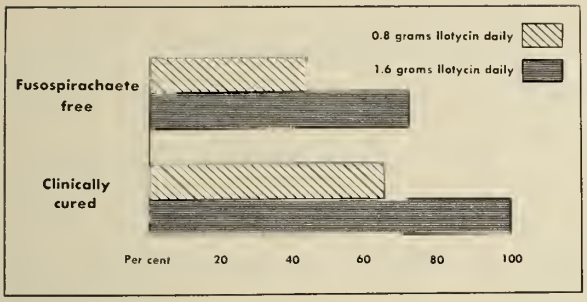

Fig. 1. Ilotycin (erythromycin) treatment of fusospirochetal infections of the mouth.

Figure 1 presents a graphic comparison of results in the two groups.

TOXICITY

Only 2 of the 32 cases evidenced a toxic reaction, which took the form of a gastrointestinal irritation. This appeared in 1 case on the second day of treatment after 2.4 gm. Ilotycin, and in the other on the fifth day after 4.0 gm. Ilotycin. The first case developed persistent nausea and vomiting that required cessation of the drug; the second a mild diarrhea.

DISCUSSION

In 1941 Chapman and Harris[1] reported experiments supporting the hypothesis that gingivitis and fusospirochetal infection of the mouth might be systemic rather than local in origin. Monkeys on a diet deficient in ascorbic acid or vitamin B or both, spontaneously developed a breakdown of oral and gingival mucous membranes. A high percentage showed invasion by fusospirochetal organisms. In contrast, monkeys with normal nutrition resisted bacterial invasion even after severe local trauma.

Approximately 50 per cent of the several hundred cases of gingivitis observed in our clinic have shown an increase in fusospirochetal organisms. It is recognized that increase in fusospirochetal organisms in mouth flora is secondary.[1,2] Conditions accepted as predisposing causes include poor or inadequate diet,[1,2,4] exhaustion, bismuth or mercury and lead poisoning, local injury, primary infections such as measles and those due to streptococcus, and malignancies.

Clinical observations of humans indicate that in gingivitis a therapeutic approach directed primarily at the fusospirochetal invasion yields poor and incomplete results.[3] Although numerous agents effect prompt decrease in the fusospirochetal flora, healing of the mucous membrane of the mouth is slow, incomplete, and associated with many recurrences. Attempts to correct a theoretical predisposing cause without also attacking the secondary invaders result in slow resolution of the disease. For best results, treatment of gingivitis with fusospirochetal infection must include the elements of (1) removal of predisposing cause, and (2) a drug or antibiotic that inhibits fusospirochetal flora.

Penicillin, aureomycin, and terramycin[5–10] have been demonstrated to be effective agents against fusospirochetal organisms. Ilotycin,[11,12] an antibiotic derived from a strain of Streptomyces erythreus, apparently has a wide antibacterial spectrum. In many respects the field of antibacterial use is comparable to that of aureomycin and other similarly derived antibiotics. Thus far, experience in our clinic suggests that the therapeutic uses of Ilotycin may be extended to fusospirochetal mouth infections.

SUMMARY AND CONCLUSIONS

Thirty-three cases of bacteriologically proven fusospirochetal infections of the mouth were treated with Ilotycin; 27 were followed adequately.

Nineteen cases that received 1.6 gm. Ilotycin per day in divided doses manifested 100 per cent clinical cures and 72 per cent bacteriological cures in 48 to 72 hours. Two instances of Ilotycin gastrointestinal toxicity were observed.

These findings indicate the desirability of further experimental use of Ilotycin, with studies based on larger numbers of cases with consequent increased reliability in percentages.

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Pathogenesis of Tuberculous Ulceration of Colon and Rectum

A Preliminary Report

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TUBERCULOUS ULCERATION of the colon and rectum is now a rare proctologic entity. Although at one time considered one of the most common causes of large bowel ulceration, increased knowledge of ulcerative colitis and amebic proctitis has relegated the tuberculous lesion to the class of uncommon conditions. Indeed, Martin[1] has stated that tuberculous ulceration of colon and rectum is seen only in late stages of the disease and forms only part of the general picture of latent pulmonary tuberculosis.

With the large numbers of tubercle bacilli in the alimentary tracts of pulmonary tuberculosis patients, one wonders why the incidence of ulceration is as low as it is. At Municipal Tuberculosis Sanitarium in Chicago, Martin and Sweany[2] reported that the incidence of virulent tubercle bacilli recovered from the stool of the patient population is 30 per cent. If one is to believe that these bacteria penetrate or permeate the mucosa, the question might arise, "Why does the tubercle bacillus not invade the colo-rectal mucosa more often than it does?"

The pathologic picture of ulcerative tuberculosis of the bowel is well known. The lymph-follicles become hyperplastic, and elliptical or circular in outline. The top is elevated above the surrounding mucosa. The striking characteristic is that the lymph follicle becomes visible and easily identified while in the normal mucosa such follicles cannot be identified grossly. Ulceration begins early while the follicle is yet small. Later the mucosa on top of the plaque breaks down at its center and the mass becomes necrotic. When the ulcer is 4 to 5 millimeters in diameter the edges are moderately thickened as a result of marginal infiltration. These small ulcers coalesce and form large ragged surface lesions. The infection follows the course of the lymphatics as it extends. The undermining of the tissue at the edge of the ulcer and the existence of submucous tracts connecting adjacent ulcers are both due to the involvement of the submucous lymphatic channels. The ulcers have been seen to lie longitudinally or transversely with respect to the longitudinal direction of the bowel.

The ulcers vary in size from a few millimeters to several centimeters. Their outline is irregular and the edge is usually reddened, thickened and slightly raised. The ulcer base is covered with a yellow pyogenic membrane. This is only slightly adherent and on swabbing, tuberculous granulation tissue is revealed. The mucosa between ulcers may be edematous, often reddened and at times dry and atrophic. It is generally normal except for vascular change. This phenomenon gives a diffusely mottled appearance to the bowel wall. The gross pathologic sequence is hyperemia, edema, follicular lymphoid hyperplasia and ulceration.[3] Microscopically the submucosa and subserosa are usually first involved. Epithelioid cells are characteristically laid down around one or more giant cells of the Langhan's type. Caseation may or may not be present and the tubercle is perimetered by lymphocytes (figure 1). Occasionally the tubercle bacillus may be seen. It is a rare occurrence when loss or partial loss of the lining epithelium

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[*] This article is an abstract of the thesis by Dr. Jackson in partial fulfillment for the degree of Master of Science in Proctology at Temple University Medical School, Philadelphia, Pennsylvania.

is seen prior to the formation of the tubercle. Ulceration usually occurs following caseation and necrosis of the tubercle. Certainly the bacilli may invade through minute abrasions in the mucosa, but with the incidence of tuberculous ulceration relatively small as compared to the incidence of virulent tubercle bacilli in the bowel, the question arises: "How does this organism invade the protective epithelial lining of the bowel?"

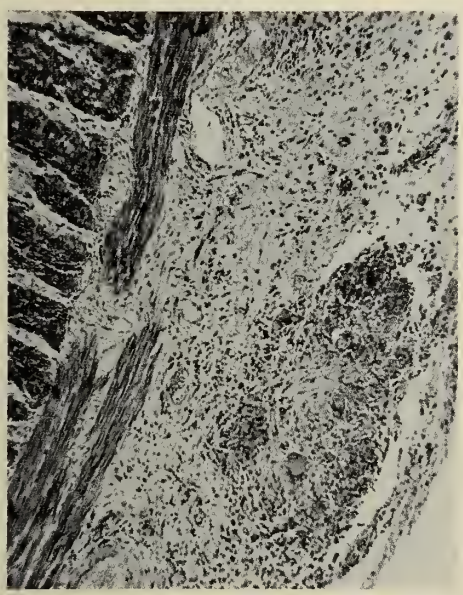

Fig. 1. Tubercle in wall of the bowel. Note giant cells and epithelioid cells. There is one area of early caseation.

It was the opinion of Cobbett[4] in 1917, that a larger number of tubercle bacilli were required to produce infection by ingestion than by inhalation. Fourteen years prior to this, von Behring[5] stated that the bowel mucosa of a young person is more permeable to the passage of tubercle bacilli than is the mucosa of an adult. With these facts in mind it was decided that a young animal susceptible to the tubercle bacillus be used in experimentation; that a relatively larger dose than necessary to give the animal pulmonary tuberculosis be injected directly into the bowel.

These observers expected to find ulceration or granulomatous reactions in the animals employed.

METHOD

The guinea pig was used in these experiments as this animal has no natural immunity to tuberculosis. The bacillus employed was H 37 R.V. This particular strain is a human attenuated form, and although relatively innocuous to humans, is still virulent to the guinea pig. Bacilli from this colony had previously caused tuberculosis in guinea pigs in one month by intraperitoneal injection.

Fifteen animals were used. All were negative to the tuberculin skin test.

On five animals a loop sigmoidostomy was performed in order to divert the fecal stream. Forty-eight hours later 1 cc. of a suspension of tubercle bacilli (approximately 1000 organisms) was injected into the distal loop. This was repeated seven days later. Two animals were sacrificed at four weeks, two at six weeks, and the fifth at eight weeks.

On five other animals, the same quantity of H 37 R.V. was instilled directly into the rectum. Here the bacilli were in direct contact with the fecal flora. This was repeated in seven days. In six weeks two animals were sacrificed, two more at eight weeks, and the fifth at nine weeks.

A laparotomy was carried out on the five remaining guinea pigs. Into the proximal large bowel 1 cc. of the H 37 R.V. suspension was injected. In eight weeks all were sacrificed.

During the course of the experiments the animals were fed a diet rich in protein and supplemented by leafy vegetables. None of the animals lost weight. In some cases an actual weight gain was observed. All animals became tuberculin positive.

At autopsy, the thorax and abdomen were thoroughly explored for evidence of gross infection in organs and lymph nodes.

FINDINGS

In none of the animals was there found gross evidence of pulmonary tuberculosis. The liver remained healthy in appearance in all cases and there was no abdominal lymphadenopathy. The large bowel was opened in its entirety and there was no macroscopic evidence of tuberculous infection. All doubtful tissue was submitted to the pathologist for histopathological study. The report in all cases was negative.

DISCUSSION

According to Aschoff, tuberculous ulceration in the bowel is caused by areas of caseation in the submucosa, breaking through the mucosa. This is easily demonstrated histopathologically. It was Medlar's[6] opinion that tubercle bacilli could permeate the intestinal mucosa without ulceration being left behind. This author also stated that local ulcerative lesions could heal and involved lymph nodes recede when tubercle bacilli cease to be fed into them from a peripheral source.

Inasmuch as it is a moot point just how the tubercle bacillus crosses the epithelial barrier of the bowel, the question arises as to whether there is not another more common manner in which the submucosa first becomes involved, then ulcerating the mucosa.

Certainly on the basis of the limited work herein described, no tuberculous lesions were demonstrated after direct instillation of virulent bacilli directly into the bowel. The ability of this particular strain to permeate the healthy mucosa of the guinea pig may be questioned. That the animals became tuberculin positive suggests that at least some chemical constituent of the bacillus was absorbed. Be that as it may, the transgression was not accompanied by gross tissue destruction.

In 1933, Wilson[7] demonstrated a tuberculous bacillemia in patients with pulmonary tuberculosis. This varied from 10 per cent to 40 per cent in varying stages of the disease. Since tuberculous ulceration of the colon and rectum is seen as a late manifestation of the disease, and since no ulceration was produced in these limited experiments, perhaps the important factor involved is tuberculous bacillemia rather than permeation. There is also the anatomical fact that the submucosa and subserosa (where the tubercle first appears) have the richest blood supply of the bowel wall.

CONCLUSIONS

The experimental work done here involved the use of guinea pigs, and the research was limited in its scope. Nevertheless, results suggest that submucosal involvement of the colon and rectum may not be brought about by permeation of the mucosa, but by tuberculous bacillemia. At the same time it is appreciated that the findings and conclusions may be markedly altered if a more virulent strain of human tubercle bacilli be employed on other laboratory animals. On the basis of this work the authors feel that further investigations should be carried out in order to establish more clearly the pathogenesis of ulcerative tuberculosis of the colon and rectum.

The authors wish to acknowledge the valuable assistance of Dr. Earle H. Spaulding, professor of bacteriology and head of department of microbiology at Temple University Hospital.

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active pulmonary tuberculosis and bronchogenic carcinoma may coexist coincidentally or in the relation of cause of effect. From postmortem studies at Ancker Hospital, St. Paul, of 4 patients who had both diseases simultaneously, William F. Nuessle, M.D., of the Dakota Clinic, Fargo, North Dakota, concludes that the malignant growths activated preexisting tuberculous infections. During a twenty-five-year period at the hospital, 12,055 autopsy examinations revealed 415 instances of inactive and 726 of active tuberculosis and 96 occurrences of cancer of the lung. Thus the incidence of malignant tumor among the active tuberculosis group was 0.6 per cent, and of active tuberculosis in the cancer group was 4.2 per cent. The rates reported in the literature are 1.4 per cent and 6.4 per cent respectively.

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Tuberculosis Control Programs in Michigan Colleges

Academic Year 1950-1951

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This third survey of tuberculosis control programs in Michigan colleges is a continuation of the studies reported in the spring of 1950 and 1951. In continuing the studies another year, it was hoped that a more complete and accurate picture of the effort for tuberculosis control in the colleges in the state might be secured and that more colleges might be stimulated to establish a regular tuberculosis screening program of some sort as a part of their program of health service.

Questionnaires were mailed to 49 of the 59 institutions of higher learning in Michigan, which include public colleges and universities, community or junior colleges operated by public school districts, and non-public colleges. Ten schools were not included for varying reasons. Some had no resident student group; others were postgraduate schools solely; two colleges, one of them newly organized, were on a revised list received after the mailing was completed.

TABLE 1
COVERAGE AND RESPONSE
(Three Years Compared)

Year	*Number of colleges included*	*Number of replies received*	*Per cent of response*
1948–49	57	41	71.9
1949–50	48	31	64.5
1950–51	49	39	79.6

Of the 39 colleges returning questionnaires this year, 30 reported tuberculosis control programs. Among the nine with no screening program for tuberculosis, one reported cooperation with mobile x-ray unit drives in the city; one had a requirement of a medical certificate showing freedom from tuberculosis for admittance and one a tuberculin test requirement in the health examination of entering students.

TABLE 2
FREQUENCY OF PROGRAMS REPORTED

	Number of colleges
Annual	18
(All students, 13; new students, 5)	
Biannual	6
Depending on availability of mobile unit	5
Report not clear	1
Total	30

Most colleges report screening for tuberculosis as a regular annual feature of their health service program.

TABLE 3
SCREENING PLAN

	Number of colleges
X-ray inspection alone as initial screen	22
Tuberculin test with x-ray film of reactors	4
Both tuberculin test and x-ray film initially	4

TABLE 4
PARTICIPATION IN SCREENING PROGRAMS

	Number of colleges
STUDENTS	
Required for all students	11
Required for new students	5
Voluntary for all students	14
FACULTY AND EMPLOYEES	
Required for all	3
Required before employment	4
Voluntary	14
No report	9

The practice relative to participation in screening programs varied. More than half of the colleges required participation for all students annually or on admission. Fewer than one fourth of them required x-ray films for all faculty and employees, the majority of these only before

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employment. On the other hand, more than one fourth made no report, by which it may probably be assumed that they do not include faculty and employees in the screening program at all. Yet two active cases were found among 2,021 faculty and employees x-rayed as against 20 among 37,533 students.

Methods of assuring participation in the required programs also varied. Five colleges make it a part of the registration procedure; nine check class lists and notify or send for students; one assesses a $5.00 delinquent fee; one withholds grades; and two make x-ray film a condition of employment.

TABLE 5
X-RAY FACILITIES

	Number of colleges
College owned	3
Mobile unit from state department of health	17
Mobile or portable unit from county tuberculosis association	6
Sanatorium mobile unit	2
No report	2

Only the largest colleges and universities own x-ray equipment. By far the majority depend on state health department or community mobile units for screening x-ray films.

For follow-up and subsidiary service colleges relied upon local sanatoriums, local hospitals, and county or city health departments. One large institution used the mobile unit of the local sanatorium to supplement its own equipment at fall registration.

TUBERCULOSIS EDUCATION

Twenty-five of the 30 colleges reporting tuberculosis control programs indicated provision for some type of tuberculosis education. Some used every opportunity for such instruction — in regular courses of study, in preparation for the screening program, and with follow-up x-ray films. Eighteen colleges planned to reach all students with tuberculosis information. Fourteen included faculty members. Five failed to indicate any tuberculosis education effort.

SCREENING PROGRAMS

Of the 30 colleges reporting that they have tuberculosis control programs, 26 indicated having had screening programs in 1950-51.

From this tabulation it is seen that more than three of every four colleges reporting programs had a program in 1950-51. All of those having none had enrollments under 500. By comparison, in 1949-50 more than half of the colleges reporting programs had not had screening programs that year and of these there were some in all enrollment groups.

TABLE 6
COLLEGES REPORTING TUBERCULOSIS PROGRAMS GROUPED BY SIZE

Enrollment	*Number of colleges reporting programs*	*Number of programs reported for 1950-51*
Over 2,500	5	5
1,500 to 2,500	4	4
500 to 1,500	11	11
Under 500	10	6
Total	30	26

TABLE 7
PEOPLE COVERED BY 1950-51 SCREENING PROGRAMS

	Students	*Faculty and employees*
Total in 30 colleges reporting programs	101,000*	11,500*
Total in 26 colleges with program in 1950-51	100,000*	11,350*
Reported screened by tuberculin test or x-ray films	37,533	2,021
Per cent in 26 colleges screened in 1950-51	37.5	17.8

*Approximate totals

Reports on the disposition of the active cases showed 23 in a sanatorium for treatment and three returned home for treatment. The questionnaire did not allow for a clear indication on whether these cases returned home for treatment in the home or to enter a sanatorium near home.

TABLE 8
ACTIVE CASES IN RELATION TO GROUPS SCREENED AND NOT SCREENED

	Number of students, faculty and employees	*Number of active cases*
Total in 30 colleges reporting programs	112,500	26
Screened in 26 of 30 colleges	39,554	22
Unscreened in 30 colleges	72,946(a)	4

(a) 55,800 of this total are students in the five colleges that screen new students only and 4,150 are faculty and employees in four colleges that require x-ray films before employment only, all of whom therefore have been x-rayed once at the beginning of their association with the college.

Based on these figures the ratio of active cases among the groups reported screened was one to 1,800. The average ratio for the United States is three or four active cases for every 1,000 people. Among the unscreened it was roughly one

TABLE 9
LIST OF COLLEGES RECEIVING QUESTIONNAIRE
(Academic Year 1950-51)

PUBLIC COLLEGES AND UNIVERSITIES
- °Central Michigan College, Mt. Pleasant
- Ferris Institute, Big Rapids
- °Michigan College of Mining & Technology, Houghton
- °Michigan State College, East Lansing
- °Michigan State Normal College, Ypsilanti
- °Northern Michigan College, Marquette
- °University of Michigan, Ann Arbor
- °Wayne University, Detroit
- °Western Michigan College, Kalamazoo

COMMUNITY AND JUNIOR COLLEGES (Public)
- °Bay City Junior College, Bay City
- †Benton Harbor Junior College, Benton Harbor
- °Flint Junior College, Flint
- Gogebic Junior College, Ironwood
- °Grand Rapids Junior College, Grand Rapids
- °Henry Ford Community College, Dearborn
- Highland Park Junior College, Highland Park
- †Jackson Junior College, Jackson
- †Muskegon Junior College, Muskegon
- °Port Huron Junior College, Port Huron

NON-PUBLIC COLLEGES
- °Adrian College, Adrian
- °Albion College, Albion
- Alma College, Alma
- °Aquinas College, Grand Rapids
- °Calvin College, Grand Rapids
- Cranbrook Academy of Art, Bloomfield Hills
- †Detroit College of Law, Detroit
- °Detroit Institute of Technology, Detroit
- Duns Scotus College, Detroit
- °Emmanuel Missionary College, Berrien Springs
- °General Motors Institute, Flint
- Great Lakes College, Detroit
- °Hillsdale College, Hillsdale
- °Hope College, Holland
- °Kalamazoo College, Kalamazoo
- †Lawrence Institute of Technology, Highland Park
- †Madonna College, Plymouth
- °Marygrove College, Detroit
- °Mercy College, Detroit
- Nazareth College, Nazareth
- Olivet College, Olivet
- †Owosso Bible College, Owosso
- °Sacred Heart Seminary, Detroit
- °St. Joseph's Seminary, Grand Rapids
- †St. Mary's College, Orchard Lake
- °Siena Heights College, Adrian
- †Spring Arbor Junior College, Spring Arbor
- °Suomi College and Theological Seminary, Hancock
- °University of Detroit, Detroit
- Western Theological Seminary, Holland

° Reported tuberculosis program
† Reported no program
No asterisk – no report received

to 18,000. Applying the ratio for the screened groups to the unscreened, the estimated number of active cases among these 72,946 might be expected to be 40 instead of the four reported.

PLANS FOR THE 1951-1952 ACADEMIC YEAR

Response to this final question in the survey reports from the 39 colleges that returned the questionnaire is: 23 – programs, 12 – no programs, 4 – no reports. Among the 23 with programs are three colleges that have not previously screened their students. Among the 12 without programs are the six that have biennial programs. Four others that reported no programs or did not report, depend for screening service on the State Health Department mobile units which are not always scheduled annually in all communities having colleges.

CONCLUSIONS

With almost 80 per cent of the colleges returning the questionnaire, the response in this year's survey was the best in the three years of the study. It is encouraging also that for the 1951-1952 academic year three colleges are being added to the ranks of those providing tuberculosis screening service for their students.

Although the information gathered through the questionnaire is not complete and does not warrant definite evaluation or conclusions, it is hoped that it may serve to bring attention to the problems preventing complete screening and desirable follow-up for tuberculosis control in the colleges and that gradually solutions for these may be found.

Quoting from *A Health Program for Colleges, Report of the Third National Conference on Health in Colleges,* published by the National Tuberculosis Association:

"The ideal program of tuberculosis control for a college calls for tuberculin testing of all new students with annual retesting of non-reactors; for the chest x-ray of all new students regardless of their reaction to tuberculin and for the annual chest x-ray of all tuberculin reactors . . . .

"There are two satisfactory modifications of the ideal, either of which will screen out those students requiring further study because of suspicious chest x-ray findings . . . .

1. Tuberculin testing with chest x-ray for all reactors. The procedure in this type of program is identical with that of the ideal program, except that it provides for the chest x-ray of tuberculin reactors only. Non-reactors are retested annually and reactors are x-rayed annually.

2. Routine chest x-ray without tuberculin testing. By this procedure, all students receive annual x-rays of the chest.

"The inadequacy of including only students in the college tuberculosis control programs has been demonstrated frequently . . . . Colleges should extend tuberculosis case-finding programs to members of the college administration, faculty and other employees, wherever such plans can be provided."

It is recommended that copies of this report be distributed to all colleges in the survey and to all tuberculosis associations in the state.

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.*

Some Studies on Experimental Diabetes*

The Tenth Annual Journal-Lancet Lecture

DWIGHT J. INGLE, Ph.D.

THIS PAPER is principally concerned with heteropoietic factors affecting carbohydrate metabolism. The word "heteropoietic" means "to cause differences." It was introduced by me[1] to focus attention upon those intrinsic and extrinsic variables which tend to cause differences in the outcomes of laboratory and clinical research. In my laboratory we are interested in any means of either exacerbating or ameliorating experimental diabetes in the rat. In addition to a brief review of heteropoietic factors in the field of experimental diabetes, I shall give an account of some of our own studies.

Although there are a number of methods of causing experimental animals to develop hyperglycemia and to waste glucose into the urine, it is doubtful that any form of experimental diabetes mellitus fully simulates the disease as it occurs in man.

REVIEW

I. *General Heteropoietic Factors*

The following list of heteropoietic factors in carbohydrate metabolism is incomplete and but few illustrative examples are given.

1. *Genetic.* Species differences in the manifestation of diabetes are well known. Mild diabetes follows complete pancreatectomy in the herbivorous goat[2] and duck,[3] but is severe in the carnivorous dog and cat. Strain differences in the sensitivity of the rat to pancreatectomy have been described.[4] Even in highly inbred strains of rats the individuality of the animal is never reduced to a point which permits the metabolic behavior of the group to be predicted reliably by the metabolic behavior of the individual.

2. *Tissue.* The metabolic behavior of individual organs and tissues differs according to their functions. Only the liver and perhaps the kidney can form carbohydrate from non-carbohydrate sources. Unlike other tissues the brain of the diabetic animal continues to oxidize glucose at an apparently normal rate.

3. *Sex.* Houssay[5] has shown that female rats are more resistant to the production of diabetes than are male rats. This sex difference is reduced by castration.

4. *Muscular activity.* Physicians know that their diabetic patients require less insulin during periods of greatly increased muscular exercise. Laboratory data which complement these observations on man will be shown in this paper.

5. *Diet.* The voluntary food intake of man and of laboratory animals is likely to be irregular and can be affected by changes in experimental conditions. The extent of glycosuria is modified by changes in both the nature and load of the diet. In our experiments on diabetes, the intake of food is kept constant by the technique of force-feeding by stomach tube. Some relationships of food intake to the manifestation of glycosuria will be discussed in later sections of the paper.

6. *Time.* The three general factors involved in the time-response relationship are: (a) the latent period required for a metabolic response to a stimulus to become full-blown; (b) physiological rhythms such as sleep, voluntary activity, feeding, sex cycles, and liver cycle; and (c) adaptation, one of the most basic characteristics of living organisms.

7. *Stressors.* These are the factors which tend to cause a harmful state of altered homeostasis in the organism (stress). In my limited experience there is no characteristic effect of non-specific stress upon

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diabetes. Selye[6] has considered that exacerbation of diabetes should ensue since non-specific stress causes activation of the anterior pituitary-adrenal cortex axis so that increased amounts of cortisone-like compounds are secreted into the blood. It is true that infections and occasionally a trauma may cause exacerbation of diabetes in patients. There is no proof that this is mediated by the adrenal cortices although the possibility cannot be discounted. In the mildly diabetic rat we find that many noxious agents tend to suppress glycosuria to a small extent. Exposure to cold or to severe exercise may cause a striking suppression of the glycosuria. Toxic amounts of ethylenediamine may cause exacerbation of diabetes in the partially depancreatized rat. This whole problem of the effect of stressors upon the diabetic state is of special interest to me and some pertinent data will be presented.

II. *Methods of Causing or Exacerbating Experimental Glycosuria.*

A survey of the large number of means of causing or intensifying experimental diabetes serves to expand our list of heteropoietic factors in carbohydrate metabolism.

1. *Pancreatic (insulin) insufficiency.* The classical means of producing experimental diabetes is by pancreatectomy. The destruction of the beta cells of the pancreatic islets by the administration of alloxan and related compounds is an equally useful tool for the production of insulin insufficiency. The following methods are of theoretical interest. The feeding of a high caloric diet to partially depancreatized, non-diabetic dogs can cause degenerative changes in the islets and ensuing diabetes.[7] The parenteral administration of a high glucose load can cause degenerative changes in the beta cells of the pancreatic islets and even diabetes in the normal cat.[8] It is important to recognize that prolonged hyperglycemia does not uniformly cause demonstrable damage to the beta cells in the normal animal. The report of Mirsky and co-workers[9] that partially depancreatized, non-diabetic dogs develop glycosuria following the prolonged administration of insulin requires confirmation. Ingle and co-workers[10] have reported the production of temporary glycosuria by abruptly stopping the prolonged injection of insulin in normal force-fed rats. A possibly related clinical phenomenon is the temporary hyperglycemia which occurs following the removal of islet-cell adenomas from patients having hyperinsulinism.[11] It is probable that the secretion of insulin by the normal pancreas is suppressed during hyperinsulinism and that when the cause of the hyperinsulinism is abruptly removed the islets remain hypoactive for a time.

2. *Diabetogenic action of hormones.* Under one set of experimental conditions or another most hormones affect the tolerance of certain animals for carbohydrate. The available preparations of anterior pituitary growth hormone are diabetogenic[12], especially in the dog and cat. Corticotropin and the 11-oxygenated steroids of the adrenal cortex are diabetogenic in rats and men but cats and dogs are more resistant. The diabetogenicity of steroid compounds can be arranged in the following descending order of potency: hydrocortisone, cortisone, corticosterone, and 11-dehydrocortisone. Lazarow[13] has shown that the diabetogenic effect of cortisone, hydrocortisone and of corticotropin in the normal force-fed rat can be potentiated by the simultaneous injection of glutathione. On the other hand, glutathione protects the rat against chemical diabetes induced by alloxan and related compounds.

Even such compounds as 11-desoxycorticosterone and progesterone will cause some increase in the glycosuria of the partially depancreatized rat when very large amounts are administered. Recently, we have found that the 11-oxygenation of progesterone enhances its diabetogenic activity in the partially depancreatized rat. Estrogens will cause a temporary exacerbation of diabetes in the mildly diabetic rat[14] but, according to Houssay,[5] the effect of prolonged administration of estrogen is to suppress the development of diabetes in the rat. Houssay[15] has found that thyroid substance will cause exacerbation of diabetes in the dog. Epinephrine and pitressin are capable of causing a temporary glycosuria in normal animals and it has been generally believed that the glycosuria is caused solely by hepatic glycogenolysis. In my laboratory we have shown that both epinephrine[16] and pitressin[17] have extrahepatic effects upon the tolerance of the rat for glucose.

Several years ago I studied the tolerance of normal rats for insulin. These animals were force-fed a high carbohydrate diet and were given gradually accruing doses of insulin following each feeding. We were seeking evidence for adaptation and increased tolerance for insulin. I shall never forget my astonishment when some of these animals exhibited glycosuria following the injection of 50 to 100 units of regular insulin. When I challenged my laboratory assistant to explain what I considered to be a laboratory error, she sadly set about the repetition of the study, but with identical results. During a lecture from me on the general effects of insulin upon carbohydrate metabolism and the "impossibility" that such results could be valid, my assistant requested that I repeat all details of the experiment myself. Confirmation of her results sent a more humble but still mystified investigator to the literature which recorded that the rapid but temporary hyperglycemic effect of certain preparations of insulin had been known for 25 years. Interest in this phenomenon faded after it was shown[18] that highly purified preparations of insulin failed to elicit hyperglycemia and that the hyperglycemic effect could be attributed to an impurity. During the past few years the "hyperglycemic" principle of the pancreas has been the subject of intensive studies which have succeeded in partial purification of the principle. This principle, which is apparently derived from the alpha cells of the islets and which may be a true hormone,[19] is called glucagon by some investigators.

Glucagon causes hepatic glycogenolysis but it is not clear that its entire effect upon carbohydrate metabolism is via the liver.

3. *Dietary.* Glycosuria can be caused by certain dietary changes. Lehmann[20] was probably the first to discover that dogs which suddenly received a large carbohydrate meal following a prolonged fast may exhibit temporary glycosuria. This phenomenon, "starvation-diabetes," is probably identical with "vagabond glycosuria" as exhibited by tramps and other poorly nourished patients soon after entrance into a hospital.[21] The overfeeding of dogs with carbohydrate was found by Hofmeister[22] to cause "alimentary glycosuria." In our own studies of the force-fed normal rat, we have consistently observed glycosuria to follow a sudden shift from a high fat to an isocaloric, high carbohydrate diet.

4. *Glycogenolysis.* A temporary glycosuria can be caused by a variety of stimuli which induce rapid glycogenolysis in the liver, so that the glucose level of the blood is rapidly increased above the renal threshold. The effect of piqure, or puncture, of the floor of the fourth ventricle was demonstrated by Claude Bernard[23] in 1849. In 1878, Boehm and Hoffmann[24] reported on "Fesselungs-diabetes" in animals bound to an animal holder. The mechanisms involved in emotional glycosuria were elucidated by Cannon and co-authors.[25] A large number of drugs and toxic extracts of biologic materials are known to cause temporary glycosuria by glycogenolysis. Temporary glycosuria may follow parathyroidectomy or removal of the carotid body, hemorrhage, asphyxia, or the intravenous injection of salts ("salt-glycosuria").[26] The release of epinephrine from the adrenal medulla may play a frequent role in causing hepatic glycogenolysis but it apparently is not the sole mediating factor for all effective stimuli.

5. *Stressors.* In addition to the noxious stimuli which cause hyperglycemia and temporary glycosuria by means of glycogenolysis, certain stressors can aggravate diabetes by other poorly understood mechanisms. The insulin requirement of some diabetic patients is increased during infections and following fractures or other forms of trauma.

6. *Renal.* Phlorhizin and related compounds and uranium salts and other renal poisons can cause a lowering of the renal threshold for the excretion of glucose so that glycosuria results.

III. *Methods of Suppressing Experimental Glycosuria*

The known methods of suppressing glycosuria are fewer than the known methods of exacerbating glycosuria.

1. *Hormonal.* The effect of insulin requires no comment. Under certain conditions the administration of large doses of estrogen can decrease the insulin requirement of diabetic patients[27] and can suppress the glycosuria of animals having experimental diabetes.[5] Under other conditions the administration of estrogens can exacerbate the glycosuria of the rat[14] and the ferret.[28]

2. *Removal of endocrine glands.* Houssay and Biasotti[29] proved that extirpation of the anterior lobe of the hypophysis causes amelioration of diabetes in experimental animals and Long and Lukens[30] proved that removal of the adrenal cortices has a similar effect. Either adrenal cortical or hypophyseal insufficiency is incompatable with the full-blown manifestation of diabetes mellitus in man. The amelioration of symptoms does not, however, constitute a cure of the disease. Houssay[31] has found some decrease in the severity of experimental diabetes following thyroidectomy in the rat. Hypothyroidism may cause a slight amelioration of clinical diabetes[32] but it has not been proven that the effects of thyroid function upon diabetes are independent of accompanying changes in food intake.

3. *Drugs.* It was shown over fifty years ago that aspirin and related compounds can suppress the glycosuria and hyperglycemia of diabetic patients and of animals having experimental diabetes.[33] Aspirin was used to treat diabetes in man, without any great benefit, up to the time that insulin became available. Illustrative data will be shown in a later section of this paper. Toxic doses of other drugs may cause a slight suppression of the glycosuria of mildly diabetic animals.

4. *Muscle work.* Physicians have long recognized that when a diabetic patient performs an unusual amount of muscular work the insulin dose must either be decreased or the caloric intake increased. Data illustrating the effect of exercise upon experimental diabetes will be shown in another section.

5. *Cold.* Acute exposure to cold may cause hyperglycemia by stimulating the mobilization of glucose from hepatic glycogen but prolonged exposure to low temperature can suppress glycosuria. Data illustrating the effect of chronic exposure to cold will be shown below.

EXPERIMENTAL

1. *Studies on the Production or Exacerbation of Glycosuria.*

In my laboratory rats are routinely maintained on a uniform intake of a fluid diet administered by

TABLE 1

COMPOSITION OF FLUID DIETS

Constituent	*Medium carbohydrate* gm.	*High carbohydrate* gm.
Cellu flour (Chicago Dietetic Supply)	120	120
Osborne and Mendel salt mixture	40	40
Dried yeast (Pabst)	100	100
Wheat germ oil	10	10
Cod liver oil	10	10
Mazola oil	200	10
Vitamin K (2-methyl-1-4-naphthoquinone)	100 mgm.	100 mgm.
Casein (Labco)	160	
Starch	200	500
Dextrin	190	250
Sucrose	200	250
Egg albumin (Merck)		160
Water to make total volume of	2000 cc.	2000 cc.

stomach tube each morning and late afternoon. The composition of the diets is shown in table 1. Male rats of the Sprague-Dawley strain having an inital weight of approximately 300 gm. are used. The standard volume of diet which represents a normal caloric intake of such an animal is 26 cc. per rat per day. This volume of the high carbohydrate diet represents approximately 15 gm. per day of available carbohydrate and the same volume of the medium carbohydrate diet represents approximately 8 gm. per day of available carbohydrate.

1. *Range of carbohydrate tolerance in the normal rat.* Fasting decreases the tolerance of either animals or patients for carbohydrate. In an experiment[34] on 10 rats which were fasted for ten days, 8 cc. of high carbohydrate diet per day was the greatest amount tolerated by all of the animals without the development of glycosuria. All of the fasted rats given more than 12 cc. of diet per day developed glycosuria up to values of 4 gm. per day. In agreement with earlier studies, the administration of insulin raised the tolerance of the fasted rat only a little.[35] Starvation diabetes is not caused by hypoinsulinism.

In related studies[36] we have force-fed normal rats with high carbohydrate diet at different rates of increment until the assimilation limit was exceeded. Very large amounts of carbohydrate, far in excess of energy requirements, were tolerated by these rats before the development of alimentary glycosuria. After the limit of tolerance was exceeded, each rat excreted significant amounts of urinary glucose. An example of alimentary glycosuria is shown in figure 1. At the slowest rate of increment, 0.5 cc. of diet per day, the rats became very obese before they developed glycosuria, and on a weight basis they had a lower tolerance for overfeeding than animals given more rapid increments of diet.

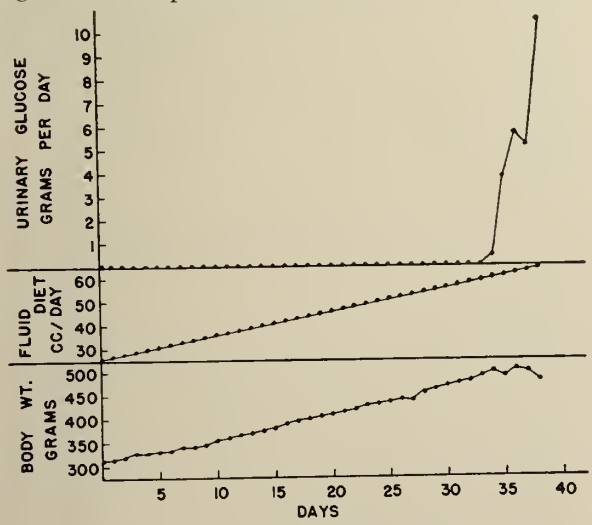

Fig. 1. Alimentary glycosuria in a normal male rat. Died on the thirty-eighth day of overfeeding a high carbohydrate diet.[36]

An important deduction which can be drawn from the above study should be emphasized at this point. Any explanation of clinical or experimental diabetes must account not only for the amount of excreted glucose but for the loss of the normal reserve tolerance for carbohydrate which lies between a normal dietary intake and the assimilation limit. The normal laboratory animal or human subject can dispose of extra carbohydrate by converting it to fat, but in diabetes this means of utilizing extra carbohydrate is decreased.[37]

2. *The diabetogenic effect of adrenal steroid compounds and of corticotropin in the normal rat.* Following observations that 11-oxygenated steroids of the adrenal cortex can intensify the glycosuria of the partially depancreatized rat,[38] Ingle and coworkers demonstrated that large doses of either hydrocortisone, cortisone[39] or of corticosterone[40] can cause glycosuria in the normal force-fed rat. Adrenal steroid diabetes tends to fade away during the continued administration of the compound and all abnormalities in metabolism disappear when administration of the compound is stopped. Animals having adrenal

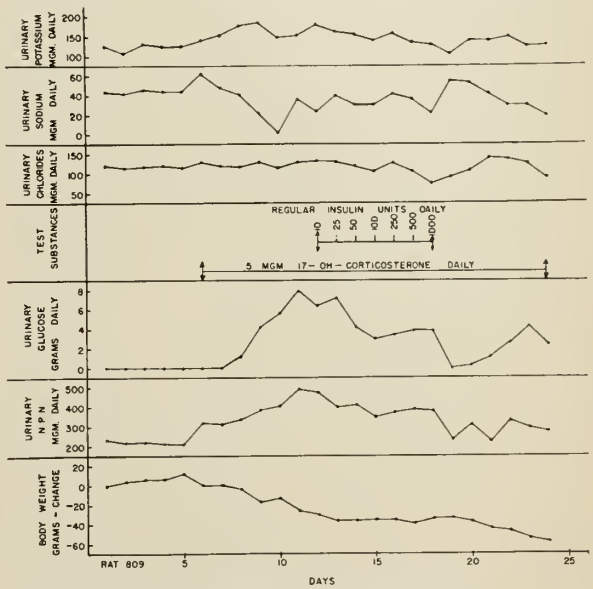

Fig. 2. Adrenal steroid diabetes with insulin resistance in a normal male rat force-fed a high carhohydrate diet.[39]

steroid diabetes may show a striking resistance to insulin (figure 2). By using the technique of continuous injection of hormones, we have been able to induce temporary glycosuria in normal rats maintained on a diet which is practically free of carbohydrate.[41] It has not been possible, in my laboratory at least, to induce glycosuria in the fasting rat by the administration of these compounds.

Although large doses of adrenal cortical hormones are required to induce glycosuria in the normal rat, it is easily possible to stimulate the adrenal cortices to secrete the activity equivalent of these amounts by the administration of corticotropin. Not only is it possible to cause adrenal steroid diabetes in the normal rat (figure 3) by the administration of corticotropin[42] but these animals can be brought to

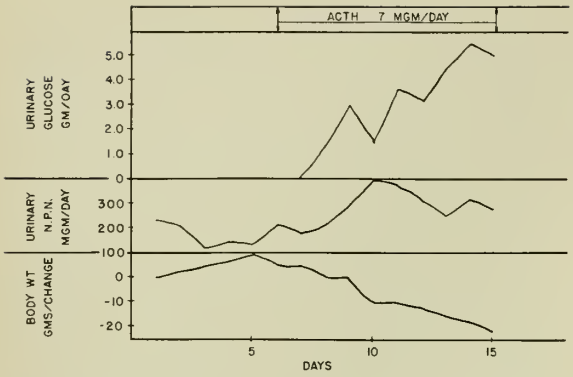

Fig. 3. Adrenal steroid diabetes induced by the intermittant injection of corticotropin in a normal male rat force-fed a high carbohydrate diet.[42]

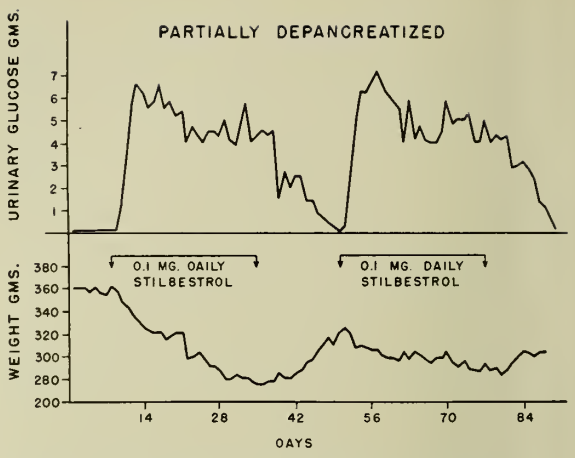

Fig. 4. Glycosuria caused by diethylstilbestrol in a partially depancreatized male rat force-fed a medium carbohydrate diet. Note the absence of spontaneous glycosuria.[14]

death by the ensuing state of hypercorticalism.[43]

The glycosuria and hyperglycemia caused by experimental hypercorticalism are accompanied by a negative nitrogen balance but the amounts of urinary glucose are much greater than can be accounted for as arising from protein when the urinary non-protein nitrogen is used as an index of gluconeogenesis from protein. One must assume that hypercorticalism either interferes with some pathway of carbohydrate utilization (either oxidation, storage or conversion to fat) or that it stimulates gluconeogenesis from fat.

Patients with clinical hypercorticalism (Cushing's syndrome) occasionally exhibit an insulin-resistant type of diabetes which disappears when the hypercorticalism is corrected by surgery of the adrenal glands. Patients who are given large doses of either cortisone, hydrocortisone or corticotropin for the treatment of rheumatoid arthritis or related diseases may, infrequently, show some decrease in glucose tolerance or, rarely, hyperglycemia and glycosuria. Diabetic patients are much more sensitive to the adrenal cortical hormones and corticotropin so that these hormones must be used judiciously. It is usually possible to control their diabetes by adjustment of insulin dosage so that the use of adrenal cortical hormones is not always contraindicated in patients with this disease.[44]

3. *Glycosuria caused by estrogens.* Estrogens are diabetogenic in the force-fed rat. Some normal rats force-fed the high carbohydrate diet have been made with estrogen to excrete glucose for a few days.[14] Partially depancreatized rats without spontaneous glycosuria and force-fed the medium carbohydrate diet have excreted the equivalent of nearly all the carbohydrate of the diet as long as the estrogen was given (figure 4). All potent naturally-occurring and synthetic estrogens which we have tested have been diabetogenic under these conditions. Estrogen causes exacerbation of diabetes only when the food intake is sustained at normal levels, for estrogen inhibits appetite in rats eating ad libitum.[45] The possibility has been tested that the diabetogenic effect of estrogen in the rat is mediated by either the adrenal cortex or the anterior pituitary. In studies on adrenalectomized-depancreatized rats[46] and adrenalectomized-hypophysectomized-depancreatized rats[47] it was shown that the diabetogenic effect of estrogen is not mediated by either the adrenal or pituitary glands.

More recently we have shown[48] that the diabetogenic actions of cortisone and of diethylstilbestrol are additive or possibly synergistic. Doses of each compound which failed to cause glycosuria in the normal force-fed rat when given alone did cause glycosuria when they were given at the same time. These results are summarized in figure 5.

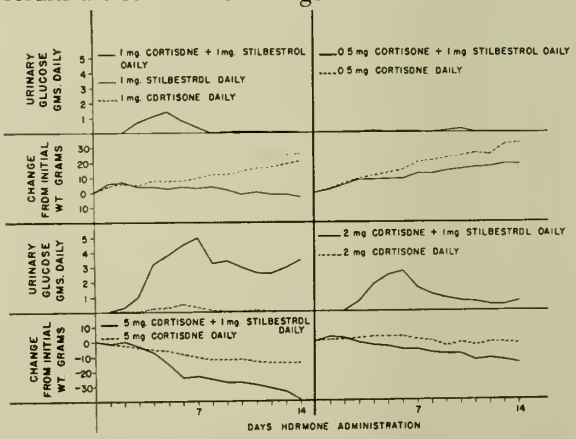

Fig. 5. The effects of diethylstilbestrol and of cortisone acetate given separately and in combination upon the glycosuria of normal male rats force-fed a medium carbohydrate diet. Averages for 6 rats per group.[48]

Dolin, Joseph and Gaunt[28] found that estrogens are effective in exacerbating the diabetes of the partially depancreatized ferret eating ad libitum. Deakins, Friedgood and Ferrebee[49] reported on one case of Cushing's syndrome in which the glycosuria was intensified during treatment with estrogen. At least some patients having diabetes mellitus show a substantial reduction in insulin requirement when treated with estrogen. Houssay[5] claims that the initial diabetogenic effect of estrogen in the force-fed rat fades away after a few weeks and that the long range

effect is to reduce the incidence of diabetes after partial pancreatectomy. We have not administered estrogen to our diabetic animals for longer than thirty days.

4. *Exacerbation of glycosuria by 11-oxyprogesterone.* In unpublished studies on partially depancreatized rats force-fed the medium carbohydrate diet we have shown that very large doses of progesterone (50 to 100 mg. per rat per day) will increase the excretion of urinary glucose in an occasional animal. The compounds, 11-ketoprogesterone, 11β-hydroxyprogesterone and 11β,17α-dihydroxyprogesterone will each intensify the glycosuria of all mildly diabetic animals at smaller dosage (8 to 16 mg. per rat per day). The compound, 11α-hydroxyprogesterone, the unnatural configuration of 11-oxygenated hormones, is ineffective. These data are illustrated in figure 6.

5. *Diabetogenic effect of anterior pituitary growth hormone.* The repeated injection of growth hormone is diabetogenic in the dog and cat,[12] but its effect in the mildly diabetic rat is relatively slight. Engel and coworkers[50] have shown that growth hormone enhances the diabetogenic effect of corticotropin when the two hormones are administered together. In my laboratory growth hormone and corticotropin have been administered by continuous injection separately and in combination to normal force-fed rats. Growth hormone potentiates the diabetogenic effect of corticotropin just as was found with cortisone. These data are illustrated by figure 7.

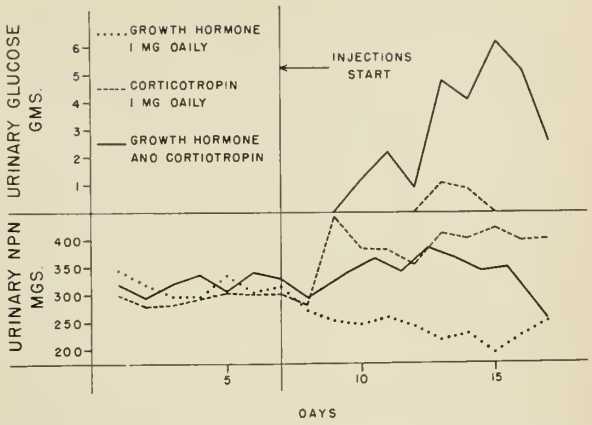

Fig. 7. Metabolic effects of growth hormone and of corticotropin given by continuous subcutaneous injection to normal male rats force-fed a medium carbohydrate diet. Each curve represents one animal from a single experimental group. (From unpublished experiments by Ingle and Li.)

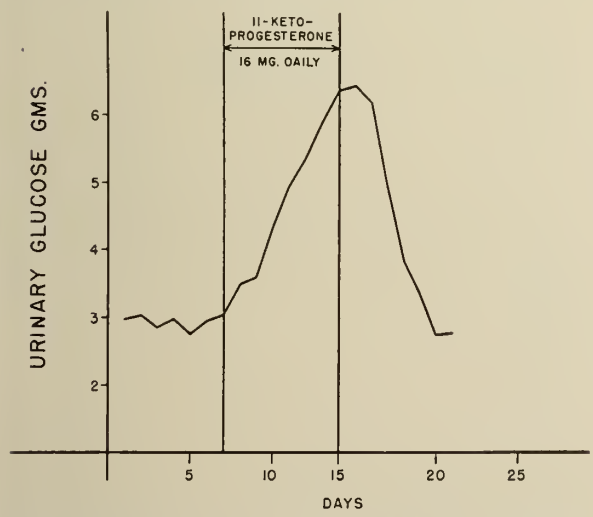

Fig. 6. Diabetogenic effect of 11-ketoprogesterone in a partially depancreatized male rat force-fed a medium carbohydrate diet. (Unpublished experiments.)

Although the available preparations of growth hormone are diabetogenic, it should not be concluded with certainty that a single principle is involved until growth hormone has been isolated in homogeneous form.

6. *Exacerbation of glycosuria by ethylenediamine.* Among the many toxic substances which we have tested for a possible effect upon glycosuria, ethylenediamine is the only one which causes an increase in the excretion of glucose.[51]

Partially depancreatized rats were force-fed the medium carbohydrate diet. Ethylenediamine (a liquid) was injected subcutaneously in amounts of 0.1 cc. daily for five days and 0.1 cc. twice daily for five days. It was tested in 5 mildly diabetic and in 5 moderately diabetic rats. As shown in figure 8, the glycosuria was intensified during the injection of ethylenediamine and then decreased to the pre-injection level when the injections were stopped.

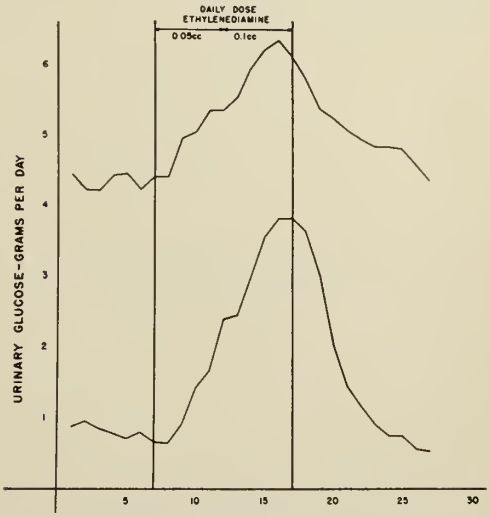

Fig. 8. Effect of ethylenediamine upon level of urinary glucose in partially depancreatized male rats force-fed a medium carbohydrate diet. Averages for 5 rats per group. Abscissa in days.[51]

II. *Studies on Methods of Suppressing Experimental Glycosuria.*

The diabetic rats discussed in this section were partially depancreatized and were force-fed the medium carbohydrate diet.

1. *Suppression of glycosuria by aspirin.* Prior to the isolation of insulin, salicylate and related compounds were occasionally used to treat diabetic pa-

tients. The first published reports appeared in 1876. The literature has been reviewed.[33] There is no convincing evidence that aspirin is of real value in the treatment of diabetic patients although there is some suppression of glycosuria and hyperglycemia.

Partially depancreatized rats maintained on the medium carbohydrate diet have been treated with large doses of aspirin. There was a marked amelioration of the glycosuria and a partial suppression of hyperglycemia. When the drug was withdrawn there was temporary exacerbation of the glycosuria to significantly higher levels than were noted during the pre-injection period. These effects are illustrated by figure 9.

2. *Suppression of glycosuria by exercise.* The effect of exercise upon glycosuria was first appreciated by physicians who observed the effects of excessive muscular activity in diabetic patients. For example, young diabetics who play tennis — some of these patients attain championship performance — find it necessary to take extra carbohydrate to prevent an insulin reaction during a strenuous match. These effects of exercise are not likely to be observed in severely diabetic patients unless treated with insulin.

We have studied the effect of forcing a diabetic rat to walk around and around the top of a metabolism cage. The animal is made to move ahead of a motor-driven plate. It is not possible to force the rat to its physiological limit of work by this device nor is this desirable. On the days that the rat is made to take extra exercise the glycosuria is decreased in proportion to the distance traveled. This is illustrated in figure 10.

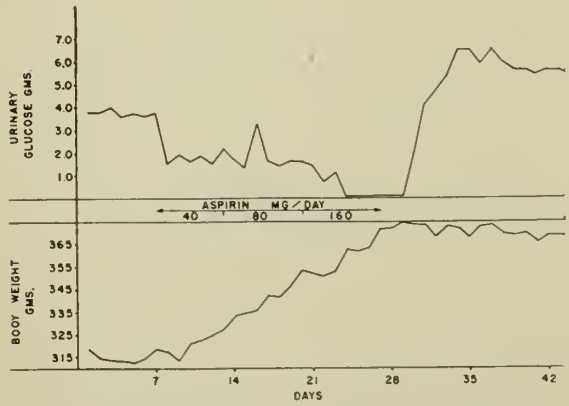

Fig. 9. Suppression of glycosuria by the subcutaneous injection of aspirin to partially depancreatized male rats[7] force-fed a medium carhohydrate diet. (From Ingle, D. J.: Proc. Soc. Exper. Biol. & Med. 75:673, 1950.)

This general effect of exercise upon the diabetic animal has been shown by another technique.[52] Normal and severely diabetic male rats were anesthetized with sodium phenobarbital and were subjected to faradic stimulation of both back legs at a rate of 5 times per second. The stimulation of muscle caused a precipitous decrease in blood glucose in both normal and diabetic rats, but to a lower aver-

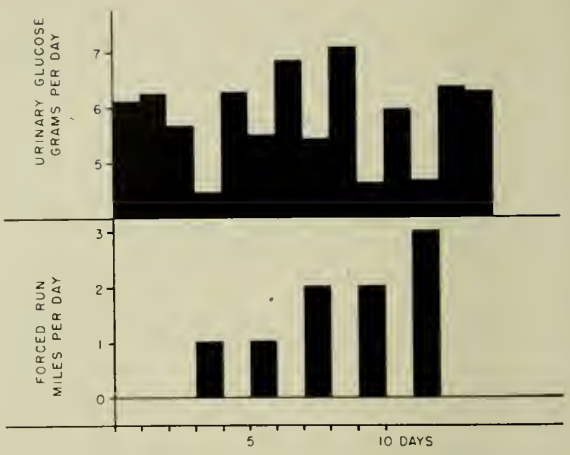

Fig. 10. The effect of forced exercise upon the glycosuria of a partially depancreatized male rat force-fed a medium carhohydrate diet.

age level in the normals. The vigorous stimulation of muscle occasionally caused fatal hypoglycemic convulsions in the normal animals and on a few occasions in the severely diabetic working animals. The effect of work on glycemia is shown in figure 11. Although the rats used in these experiments were depancreatized as completely as possible and were severely diabetic, it would be unsafe to conclude that no physiologically important amounts of insulin were present.

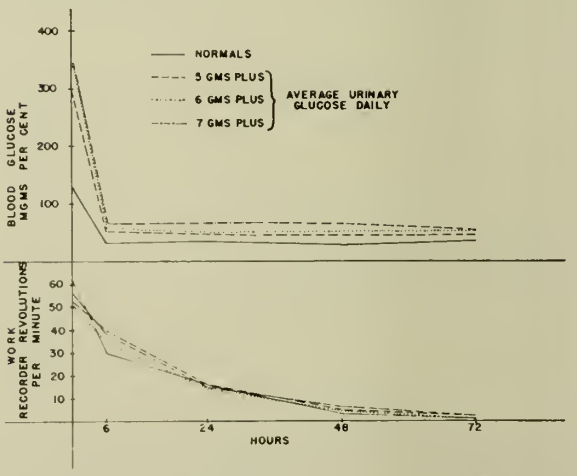

Fig. 11. Effect of stimulation of muscle upon the hyperglycemia of extensively depancreatized male rats force-fed a medium carbohydrate diet. Averages for 10 rats per group. (Figure derived from published data.[52])

3. *Suppression of glycosuria by prolonged exposure to cold.* Although hyperglycemia may be among the early responses to cold, the prolonged exposure to low temperature can suppress glycosuria in the diabetic rat. Six partially depancreatized, moderately diabetic rats were force-fed the medium carbohydrate diet. Following maintenance at 26° C. for ten days, the temperature was lowered to 16° for seven days, 10° for seven days, and 3° for ten days, and the temperature was then restored to

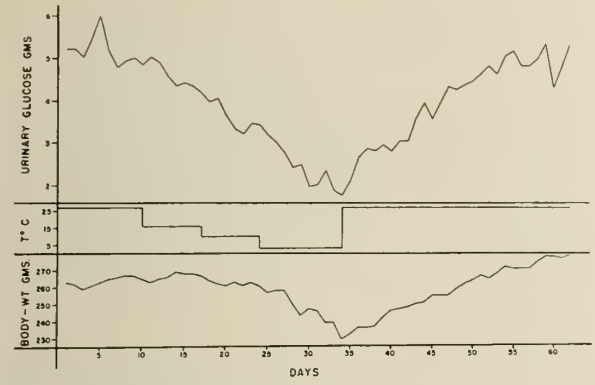

Fig. 12. Effect of exposure to cold upon the glycosuria of partially depancreatized male rats force-fed a medium carbohydrate diet. Averages for 8 rats.

26° for a second control period. The level of urinary glucose decreased gradually during exposure to cold and gradually increased to control values during the recovery period. The data are shown in figure 12. The reasons for the slow, rather than abrupt, rise in glycosuria during the recovery period is not known to us.

4. *The effect of a toxic compound upon glycosuria.* As a test of the hypothesis that any stressor should cause exacerbation of diabetes by activating the adrenal cortices we have administered a large series of toxic compounds to the diabetic rat with variable results. Most of the compounds have not had any significant effect upon the glycosuria of the rat although there is a general tendency for the mildly diabetic rat to excrete less glucose when it is brought near death by any means. The subcutaneous injection of dilute solutions of formaldehyde causes a significant suppression of glycosuria in the mildly diabetic rat.[53]

Partially depancreatized rats were maintained on the medium carbohydrate diet and were injected with solutions of formaldehyde in doses of 0.25, 0.5, and 1.0 cc. twice daily for seven days, 5 rats per dose level. There was some decrease in the level of urinary glucose in the mildly diabetic rats. When

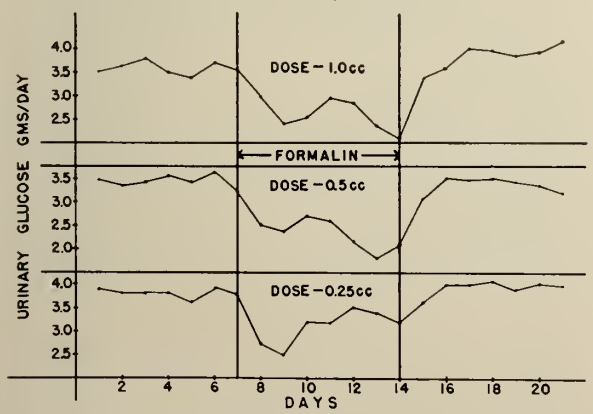

Fig. 13. The effect of injections of 1.5 per cent formaldehyde upon the glycosuria of partially depancreatized male rats force-fed a medium carbohydrate diet. Averages based upon 5 rats per group.[53]

the injections were stopped, the glycosuria was re-established at its pre-injection level. These data are shown in figure 13. The administration of identical amounts of formaldehyde to severely diabetic rats did not affect the level of glycosuria.

COMMENT

All tissues are involved in the metabolism of carbohydrate. The orderly assimilation of intermittent loads of carbohydrate during widely varying needs for energy is an impressive example of homeostasis. It is not surprising that nature can fail in more than one tissue or at more than one stage of metabolism or that the experimentalist should be able to disturb homeostasis by a variety of insults.

Table 2 represents the approximate values for the maximum carbohydrate load tolerated by rats under different experimental conditions. It is suppressed to its smallest value in the eviscerated rat[35] (no liver, pancreas or gut) under resting conditions and reaches a maximum in the intact rat which is adapted to over-feeding of the high carbohydrate diet.

Elasticity is a parameter of all biological and physical systems. I have found it entertaining to compare carbohydrate tolerance to an elastic rubber band which can normally adjust to either a large or small load but which can lose elasticity as the result

TABLE 2

GLUCOSE TOLERANCE UNDER DIFFERENT EXPERIMENTAL CONDITIONS IN THE RAT

Experimental condition	*Glucose tolerance* MG/100/H
Eviscerated, infused 24 hrs. without insulin	4
Intact, force fed normal caloric intake of high carbohydrate diet	208
Intact, force fed after 10 day fast	95
Intact, adapted to overfeeding of high carbohydrate diet	400

of overloading or by aging. Elasticity can be modified by temperature or by a large number of nonspecific chemical agents. This characterization of carbohydrate tolerance explains no specific mechanism but is merely intended to emphasize that a variety of nonspecific mechanisms can cause the same end result in both physical and biological systems. By the very nature of organized matter the number of nonspecific forces which can disturb equilibrium is very large but the number of possible general responses is relatively small.

Among our studies of heteropoietic factors affecting experimental diabetes, we screen for compounds which will modify the diabetic state. Herein the experimenter tests this and that compound, more by random selection than by reason. It is a bit more tasteful to refer to the process as the courting of serendipity. Actually serendipity implies discovery of the unanticipated while pursuing another objective. In the practice of screening, the experimenter has no objective other than the chance observation of something worthwhile. It is a useful procedure

in the field of pharmacology and I have no doubt that its continued practice in the field of carbohydrate metabolism will greatly extend our list of agents which will modify carbohydrate metabolism.

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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.*

Lutembacher Syndrome*

Edited by E. G. Huppler, M.D.,
Ben Fuller, M.D., and
John F. Briggs, M.D.
St. Paul, Minnesota

The Lutembacher syndrome is a congenital heart lesion consisting of an auricular septal defect, combined with a congenital or acquired mitral stenosis and enormous dilatation of the pulmonary artery. The auricular septal defect differs from a patent foramen ovale in that the foramen has a valve to seal off the defect, and in this syndrome there is a direct interauricular shunt. Normally the left auricular pressure is higher than the right and here the mitral stenosis in combination with this normally higher left arterial pressure produces a left-to-right shunt. The right auricle, the right ventricle and the pulmonary artery are thus enlarged while the left ventricle and aorta are relatively small. The left auricle is not enlarged because the pressure is transmitted through the shunt to the thinner walled right heart.

In early infancy the pressure may be greater in the right auricle than in the left; if so, the shunt is right-to-left and the baby may be a "blue baby" or suffer from attacks of cyanosis. With growth the pressure in the left auricle rises thus overcoming this pattern of flow. Increased pressure in the left auricle forces blood from the left auricle into the thin walled right auricle. The blood passes to the right ventricle out by way of the pulmonary artery to the lungs, and back by the pulmonary veins to the left auricle. Thereupon the increased amount of blood which has been returned to the left auricle again raises the pressure in that chamber and blood again is shunted into the right auricle. This vicious circle causes enlargement of the right auricle, right ventricle and pulmonary artery but spares the left heart and aorta.

DIAGNOSIS

Diagnosis at birth and during infancy is difficult because murmurs and clinical findings are subject to wide variation at this age.

In later life the patient has a frail build and poor physical development. The great enlargement of the right ventricle usually leads to a left-sided chest deformity. A tracheal tug may be present because of the enlarged pulmonary artery and pressure on the trachea. The small volume of blood reaching the systemic circulation causes a low pulse pressure and a low blood pressure. There may be a slight acrocyanosis but inasmuch as the shunt is left-to-right there is no deep cyanosis and no clubbing.

The murmurs in the Lutembacher syndrome are subject to variation. The most characteristic findings are a rough systolic murmur and a thrill close to the sternum at the base of the heart in the second and third interspaces. It is common to find some evidence of rheumatic valvular disease, such as apical-systolic and mid-distolic murmurs.

The pulmonic second sound is loud and snapping due to increased pressure in the lesser (pulmonic) circulation.

The enormous dilatation of the pulmonary artery may cause a relative pulmonary insufficiency with a high pitched, early diastolic murmur audible together with the left sternal border.

X-ray examination. The distinctive x-ray features are: (1) great enlargement of the right auricle and right ventricle, (2) prominent pulmonary conus, (3) small aortic knob, and (4) increased hilar shadows.

The enormous size of the pulmonary artery differentiates the Lutembacher syndrome from other defects of the auricular septum.

Fluoroscopic examination is of great help. The vascular enlargement of the hilar areas cause a true dancing hilus. The contour of the heart is characteristic but varies with the size of the pulmonary artery.

The electrocardiogram is likely to show a prolongation of the PR interval and of the QRS interval, and a right axis deviation is present.

Complications of Lutembacher syndrome are:

1. Superimposed rheumatic infection. This occurs in 60 to 75 per cent of persons with auricular septal defects and is the most common complication.
2. Subacute bacterial endocarditis. Although common in patients with congenitally malformed hearts, it is rare with a Lutembacher syndrome.
3. Cardiac arrhythmias.

*From the medical service at St. Joseph's Hospital, St. Paul, Minnesota.

4. Pneumonia, pulmonary infections and pulmonary emboli. There are frequent complications.
5. Hoarseness. Pressure on the recurrent laryngeal nerve may occur due to the large heart and the great dilatation of the pulmonary artery.
6. Venous stasis and the formation of thrombi occur secondarily to the great dilatation of the right side of the heart. These thrombi may cause pulmonary infarcts or give paradoxical emboli with cerebral accidents.
7. Pregnancy. Child rearing is remarkably well tolerated by women with this disorder.

Differential diagnosis. Lutembacher syndrome must be differentiated from:

1. Rheumatic heart disease, which may mask an auricular septal defect; the right-sided enlargement and normal sized left auricle will be of help in the diagnosis.
2. A patent ductus arteriosus, which may be confused in infants during the stage when only a systolic basal murmur is present. The pulse pressure may be of help because this is usually low with auricular septal defects.
3. Pulmonary tuberculosis, Hodgkin's disease, mediastinal tumors, and substernal thyroid can usually be differentiated by fluoroscopic examination because Lutembacher syndrome has the dancing hilus.

The surgical treatment of this disease has not been defined but such symtomatic treatments as is indicated should be instituted.

CASE REPORT

This is the case of a 21-year-old white male, who was admitted to the service of Dr. Ben Fuller at St. Joseph's Hospital, St. Paul, Minnesota, on June 5, 1952 because of headaches, fever and weakness, exertional dyspnea, and a congenital heart lesion.

Past history. The patient stated that he had known from the time of childhood that he has a congenital heart lesion. He had pneumonia at the age of 8 years, but had no further difficulty until 19 years of age. He had not had rheumatic fever nor any swelling of the joints. From the age of 19 to 21, he had taken digitalis intermittently for symptoms of congestive failure. In January 1952, he was studied at the University of Minnesota by cardiac catheterization and a definite diagnosis was made. Since January 1952 he had maintained a borderline state of compensation while he was fully digitalized.

Clinical findings. The patient's temperature was 99.6°, blood pressure 118/66, pulse 84 and irregular. The patient was underdeveloped and 102 pounds in weight. A hemorrhagic petechiae was noted in the right buccal mucosa. The liver was palpable 6 cm. below the costal margin. A precordial bulge was noted. The heart was enormously enlarged, with apex lying in the fifth interspace in the midaxillary line. The conus was enlarged to percussion. Cardiac impulses were visible at the apex as also to the right of the sternum. The mitral first sound was booming; there was an apical thrill and murmur (timing not recorded).

Red blood count was 3,950,000, hemoglobin 13.3 grams, serimentation rate 38 mm/hour. Blood and urine cultures, taken because of fever while in the hospital, were negative.

Anterior-posterior and lateral roentgenograms of the chest showed marked enlargement of the heart with great enlargement of the right side, a prominent pulmonary conus, small aortic knob and increased hilar shadows.

Fluoroscopic examination was not done, and an *electrocardiogram* was not taken.

Clinical course. After 36 days of rest, digitoxin and antibiotics, the patient was discharged in July 1952. He works at the Veterans Administration Hospital as a dictaphone operator. Here the cardiac status of patient was examined. The diagnosis established and confirmed by catheterization was Lutembacher syndrome.

If you are to infuse the young with the reading habit, you must set a trap for them, so baited that they will walk into it unaware. Books must be made accessible. It is someone's business in every medical school to teach laboratory methods to the students, but it is no one's particular business to teach them how to use medical literature, which to the majority in the long run will be infinitely more useful than an experience with smoked foxes and Ludevig's drum.

Harvey Cushing: *The Doctor and His Books*

The Continuation Medical Education Program—Notes on the Results of a Survey of Physicians

UNFORTUNATELY, there is no really accurate yardstick available for measuring the effectiveness of programs in continuation or postgraduate medical education. Any attempt to do so must take into account numerous factors, many of them quite intangible. One of these factors which can be measured to a certain extent is the reception accorded these programs by the physicians who attend them.

In an attempt to determine how the physicians of Minnesota evaluate the program in continuation medical education at the Center for Continuation Study, a questionnaire was sent to all practicing physicians in the state in the spring of 1952. Questionnaires were sent to approximately 2800 physicians, and it was requested that they be returned unsigned. Replies were received from 862 or 31 per cent. Of the respondents, 497 indicated that they were engaged in general practice, 302 stated that they limited their practices to various fields, and the remaining 63 did not answer this question. Their answers to some of the questions which were asked are presented in the accompanying tables.

Considerable caution is necessary in the interpretation of these figures. They seem to indicate, however, that of the Minnesota physicians *who returned the questionnaire* well over two-thirds had attended one or more courses at the Center for Continuation Study, had found them to be of great practical value, and felt that the speakers were good or excellent. It is to be emphasized, however, only about one-third of the questionnaires were returned. It is possible — even likely — that those physicans who failed to return the questionnaire are the ones with little or no interest in the program. For this reason, the figures given above cannot be considered representative of the opinions of all Minnesota physicians.

Criticisms were frequent, and many of them were constructive and helpful. Not infrequently contradictory criticisms were offered. For instance, some physicians felt that the courses in general presented too much fundamental material while others believed that they were not basic enough. Again, some considered the speakers too dogmatic while a few felt that the lecturers were frequently unwilling to take a definite stand on controversial questions.

The most frequent criticism was that "courses are not practical enough." It is, of course, difficult to define precisely what constitutes "practical material."

PREVIOUS ATTENDANCE AT CENTER FOR CONTINUATION STUDY COURSES

Courses previously attended	*General practitioners*	*Specialists*	*Unspecified*	*Totals*
None	78 (16%)	71 (24%)	22 (36%)	171 (20%)
One	98 (20%)	76 (26%)	8 (13%)	182 (21%)
2 to 5	205 (41%)	106 (36%)	17 (28%)	328 (39%)
More than 5	114 (23%)	40 (14%)	14 (23%)	168 (20%)
Totals	495(100%)	293(100%)	61(100%)	849(100%)

GENERAL EVALUATION OF MATERIAL PRESENTED AT COURSES

Evaluation	*General practitioners*	*Specialists*	*Unspecified*	*Totals*
No practical value	0 (°)	1 (°)	0 (°)	1 (°)
Limtied practical value	109 (27%)	64 (28%)	9 (21%)	182 (27%)
Great practical value	295 (73%)	164 (72%)	34 (79%)	493 (73%)
Totals	404(100%)	229(100%)	43(100%)	676(100%)

GENERAL EVALUATION OF SPEAKERS TAKING PART IN COURSES

Evaluation	*General practitioners*	*Specialists*	*Unspecified*	*Totals*
Poor	4 (1%)	1 (°)	1 (2%)	6 (1%)
Fair	29 (6%)	21 (9%)	5 (10%)	55 (7%)
Good	274 (56%)	132 (53%)	26 (52%)	432 (55%)
Excellent	179 (37%)	94 (38%)	18 (36%)	291 (37%)
Totals	486(100%)	248(100%)	50(100%)	784(100%)

°indicates less than 1%.

It would be quite impossible to design a course containing material which all physicians would agree was purely "practical."

If, however, this could be done, would it be a desirable objective? We think not. The ideal continuation course in a medical field, we believe, is one in which fundamental principles are reviewed, practical diagnostic and therapeutic points discussed, and new and exciting developments in the field presented. Reports of pertinent clinical and fundamental investigatons are not to be avoided simply because the results cannot be put to use immediately, for of course it is the investigator's constant search which makes medicine the dynamic and fascinating field that it is.

ROBERT B. HOWARD, M.D., Ph.D.,
Director, Department of Continuation Medical Education, University of Minnesota

The Nervous System, by Frank Netter, M.D., Volume I of The Ciba Collection of Medical Illustrations. Published by Ciba Pharmaceutical Products, Inc., Summit, N. J., $6.00.

This volume is the first of a series illustrating the major anatomy and pathology of all the systems comprising the human organism. There are 104 full-color plates illustrating the five sections which make up the book: Anatomy of the Spine, The Central Nervous System, Functional Neuro-Anatomy, the Autonomic Nervous System and Pathology of the Brain and Spinal Cord. Many illustrations are simplified but are adequately comprehensive for a complete presentation of the subject matter. Others are entirely schematic and clarify points equally well.

At a time when great stress is placed upon visual aids to accompany the written word in the educational process, these illustrations with legends and descriptions by Doctors Kaplan, Kuntz and von Bonin commend themselves to all who are teaching or are learning the functions of the nervous system.

With a subject index at the back and all plates listed and paged in the table of contents in the front, this atlas should afford easy access to pertinent material and be equally valuable to the busy practicing physician as well as to the teacher and student of medicine.

I.P.

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Battle Casualties, by Gilbert W. Beebe, Ph.D. and Michael E. De Bakey, M.D., 1952. 277 pages, 100 tables. Springfield, Illinois: Charles C Thomas. $10.50.

Doctors Beebe and DeBakey have compiled a monumental set of statistics from the medical, casualty, and health records of the armed services in World War II. Concepts on the incidence and mortality of wounds as well as hospitalization and evacuation of casualties are presented.

The incidence and mortality of wounds according to causal agents, anatomical locations, extent of injury, treatments, etc., are presented. These statistics are illustrated by one hundred clear graphs and charts.

An analysis of the need for medical specialists of various types in the forward battle areas is of special interest.

This book is invaluable for those who are about to enter the armed forces and those interested in the organization of a civil defense medical program.

M.D.McM.

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Post Graduate Lectures on Orthopedic Diagnosis and Indications, volume III, by Arthur Steindler, M.D., F.A.C.S., Professor of Orthopedic Surgery, State University of Iowa, 1952. 270 pages, 372 illustrations. Springfield, Illinois: Charles C Thomas, $8.75.

In the first part of this book, Dr. Steindler discusses tuberculosis of the skeletal system. The opening chapter is devoted to a general description of tuberculosis with respect to pathogenesis, pathology, diagnosis, course, prognosis, and treatment. In the following chapters the author gives in more detail his experiences with tuberculosis of the spine, hip joint, knee, foot and ankle and upper extremity. Special emphasis is given to the fact that the recent advent of antibiotics has not displaced the time-proven surgical principles.

The last half of the book is composed of a group of lectures by Dr. Steindler on osteomyelitis. Again the first several lectures are given over to a thorough discussion of the pathogenesis, pathology, diagnosis, and treatment of both acute and chronic osteomyelitis. The final chapters are concerned with a more detailed description of osteomyelitis of the spine and pelvis as well as some of the more unusual types of osteomyelitis. It is worthy of note that Dr. Steindler stresses the point that although the antibiotics play a great role in the therapy of osteomyelitis, surgical intervention at the proper time using the prineiples laid down by doctors many years ago is still the mainstay of treatment.

This book is of special interest to orthopedic surgeons but because of the clear manner in which basie principles are expounded, it ean be recommended to all physicians.

G.N.

Physiological and Therapeutic Effects of Corticotropin (ACTH) and Cortisone, by Dwight J. Ingle, Ph.D., and Burton L. Baker, Ph.D. Springfield, Illinois: Charles C Thomas, 172 pages. $5.50.

The recent advances in medical science have revealed how markedly the body economy is dependent upon the function of the adrenal glands. The application of the steroid compounds of the adrenal cortex and corticotropin to the resolution of human disease has intensified the interest of the medical profession in the adrenal cortex and its hormones and in the influence of the anterior pituitary gland upon the adrenal cortex. The available knowledge is so extensive and the medical literature documented with so many reports that there has been a need for a concise and authoritative statement on the subject, which will summarize for the clinician the basic principles and their application to therapeutic problems. This has been accomplished in the present volume admirably well by two competent investigators in the field. They have presented in a readable manner, and in relatively nontechnical language, the basic principles underlying cortisone, hydrocortisone and corticotropin, in addition to other adrenal steroids.

The introductory chapter is concerned with a brief historical discussion, followed by a presentation of the normal physiology of the adrenal cortex and its relation to the anterior hypophysis. The chemical structures of the 11-oxygenated steroid hormones are then presented. The influence of these agents upon the body functions is also delineated. Finally, there is a discussion of the clinical application of the available drugs to human disease.

For the more inquisitive reader, there is a bibliography encompassing 324 references. The volume is not indexed, but a practical table of contents introduces the work. This valuable review can be highly recommended for the busy physician and student of medicine. Since the advancements will continue, and additional knowledge will accrue in this field, a revised edition will no doubt appear. The reviewer hopes that if another edition is forthcoming, the authors will append to the photographs of some of the pioneers in the field that are now included, a classic reference or two pertaining to each of their works.

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Herrold, R. D.: South. Clin. North America *30*:61, 1950.

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American College Health Association News . . .

THE Association welcomes two new members, which have been approved for membership by the Executive Committee:

Central State College, Wilberforce, Ohio, with a total enrollment of 1,023 men and women. The official representative to the Association is Dr. Benjamin F. Lee, college physician and health director of the Student Health Center. Dr. Harvey B. McClellan, associate college physician, is the alternate delegate. One dentist, three nurses and one technician complete the Health Service staff.

St. John College, Cathedral Square, Cleveland 14, Ohio, with an enrollment of 355 women. Miss Patricia A. Jones, B.S.N., the college nurse, is the official representative, and Miss Madeline Kingersky, M.S. in P.H.N., instructor of public health nursing, is alternate delegate. The health service staff consists of one part time physician, one part time psychiatrist, and one full time nurse.

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The Thirty-first Proceedings should have reached you. Two copies were sent to each member institution—one to the office of the director, the other to the library. In case your copy has not arrived, will you please contact the secretary. Approximately fifteen libraries thanked us for the copy last year.

Dr. Charles E. Shepard of Palo Alto, California, tackled the herculean job of editing the transcriptions recorded at the Columbus meetings. The conclusion drawn from this experience is that hereafter no transcriptions should be made and only the prepared papers need be collected for incorporation in the annual Proceedings.

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Donald S. MacKinnon, M.D., director of Student Health Service at the University of California, Los Angeles, states in his annual report that patient-visits and number of technical procedures performed increased in 1952-53 as compared with the preceding year. In preparation for the move of the Student Health Service into the new Medical Center, scheduled for the summer of 1954, the staff members now hold Medical School appointments. Arrangements are being made with the Department of Medicine to provide twenty-four-hour intern and resident coverage to care for the student patients in the Hospital unit.

The tuberculosis control program again assumed its usual place as a major threat to the budget. Patient visits in connection with tuberculosis more than doubled. During the past year twenty-two cases of active tuberculosis were found as compared with nine for the preceding year.

° ° °

Changes in directors of student health service include:

Harry Zion, M.D., from Palo Alto, California, has replaced Glen West, M.D., at The State College of Washington, Pullman.

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News Briefs . . .

NORTH DAKOTA

About 35 physicians attended the seventh annual regional meeting of the American College of Physicians Saturday, September 12, at St. Luke's Hospital in Fargo. Presiding officer of the all-day meeting was Dr. Robert B. Radl, Bismarck, governor of the North Dakota region.

Dr. Howard P. Lewis, Portland, Oregon, regent of the College and professor at the University of Oregon Medical School, spoke on potassium disturbances in congestive heart failure, and at a dinner meeting on "Your American College of Physicians." Other speakers and subjects include: Dr. Robert B. Tudor, Bismarck, malignancies in children; Dr. Lester E. Wold, Fargo, complications of cortisone therapy; Dr. F. T. Lytle, Fargo, peripheral vascular collapse in a cardiac patient during surgery; Dr. Robert M. Fawcett, Devils Lake, insulin requirements in Kimmelstiel-Wilson's disease; Dr. Robert C. Painer, disseminated lupus erythematosus; Dr. Marshall Landa, Fargo, radioactive iodine in the diagnosis of thyroid disease.

The next regional meeting of the College will be in Bismarck, September 11, 1954.

* * *

A team of specialists from the USPHS laboratory in Atlanta, Georgia, were in Devils Lake during the last week in August to check the appearance of amebic dysentery in Benson and Ramsey counties. At that time there had been 12 cases of the disease reported, with one death. Laboratory facilities for the USPHS team were set up at Devils Lake under the direction of Dr. John Fawcett, director of Lake District Public Health Unit.

Dr. H. Milton Berg, head of the radiology department of the Quain and Ramstad Clinic in Bismarck, presided at the fifteenth conference of the Rocky Mountain Radiological Society held in Denver the last of August. Dr. R. F. Nuessle, of the department of surgery of the Quain and Ramstad Clinic, spoke on "Tumors of the Small Bowel."

* * *

Dr. Carl I. Rollefson, who has been a physician of the North Dakota State Hospital since 1941, resigned from his post on September 1.

MINNESOTA

Dr. William C. Bernstein, St. Paul, is the new president of the Southern Minnesota Medical Association. Dr. C. P. Anderson, Austin, is the new vice president, and Dr. Charles Stroebel, Rochester, secretary-treasurer.

* * *

Two physicians have recently appeared as Town Toppers in the Minneapolis *Star* — Dr. Henry L. Ulrich and Dr. A. E. Benjamin. Dr. Ulrich, a graduate of Johns Hopkins Medical School, is a professor emeritus of the University of Minnesota Medical School and has a record of 51 years of continuous practice in internal medicine in Minneapolis. Dr. A. E. Benjamin, a graduate of the University of Minnesota Medical School in 1892, is also a professor emeritus of that school, and has practiced for more than 60 years in Minneapolis.

* * *

Dr. Rudolph Hultkrans is the new president of the medical staff of Northwestern Hospital in Minneapolis. Other officers include Dr. Harold Miller, vice president and Dr. Robert Priest, secretary-treasurer.

The Journal Lancet

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

The Beneficial Effects of Soy Bean Products in Eczema of Infancy and Childhood

ALBERT V. STOESSER, M.D., Ph.D., AND LLOYD S. NELSON, M.D.
Minneapolis, Minnesota

Infants and children of families with allergic manifestations are always in danger of developing a sensitivity to cows' milk if this food constitutes a major portion of the diet.[1] Milk substitutes have been developed to take care of this situation. Most popular have been evaporated goats' milk, casein digests, amino acids,[2] powdered soy bean products, and preparations made of meat with added minerals,[3] but the response to these foods has not been very favorable. It was not until the introduction of a new soy bean emulsion that satisfactory results were obtained. This product was given to the individuals with eczema attending the Pediatric Allergy Clinics of the University and Minneapolis General hospitals, and both clinical and laboratory studies were made.

In a previous paper[4] it was concluded that if external treatment of the skin is of the best and a good elimination diet is employed, a soy bean food can produce a beneficial effect in eczema of infants and children both in milk-sensitive patients and in patients allergic to other foods. Another communication[5] revealed the fact that the iodine numbers of the total fatty acids of the plasma lipids might assist in determining selection of individuals who would be helped by the soy bean preparations.

Since then, investigations with the soy bean milk have been continued and now more definite information containing its value can be given. The plan of this paper is to offer a more or less routine topical therapy for eczema depending upon the type, and to present the proper use of soy bean products in connection with the feeding of the eczematous children.

The term eczema describes not a disease entity but a more or less characteristic form of cutaneous reaction producing a group of various dermatoses which sometimes closely resemble one another. Infants may have atopic, contact, seborrheic, or infectious dermatitis, and other eczematoid eruptions such as nummular eczema which cannot be classified.[6]

Atopic eczema or allergic dermatitis is the most common. It usually appears around the third month of life on the flushing areas of the face, on the neck, and flexures of extremities, especially in the antecubital fossae and in the popliteal spaces. The distribution is usually symmetrical. The earliest change in the skin is an erythema and this soon may be followed by

ALBERT V. STOESSER, *a 1925 graduate of the University of Minnesota Medical School, is on the staff of the University Hospital, Minneapolis General Hospital, and St. Barnabas Hospital. He is past president of the Northwestern Pediatric Society, former member of the board of regents of the American College of Allergists, and was assistant secretary-treasurer of the American College of Allergists.*

Aided by grants from Medical Research Fund of the University of Minnesota graduate school and the Borden Company.
Mull-Soy prepared and furnished by the Prescription Products Division of the Borden Company.

papulation, vesiculation, oozing, and crusting. The changes originate in the blood vessels of the skin adjacent to the epidermis. Erythema is due to a congestion of these vessels over a diffuse area, papulation to the escape of cells from the vessels, and vesiculation to the release of fluid. The majority of cases are exudative. However, if vesiculation is absent, the patches of eczema are flat, dry, and pale to deep red in color. They vary considerably in size, sometimes covering large areas of the skin, especially the trunk of the body. A fine scaling may be present and pruritus is usually moderate.[7]

Scratching gives rise to a punctiform appearance which is considered by some clinicians to be a diagnostic feature. Moreover, trauma may cause infiltration, fissuring, and pustulation. These secondary manifestations can become more prominent than the picture of the primary eczema.

The family history of atopic eczema most often reveals the prevalence of allergic diseases. Cutaneous tests show positive reactions in approximately one-half of the cases. There may be an egg-white sensitivity which can be detected at the onset of the eczema and probably dates back to active intrauterine sensitization or could come from a sensitivity built up by ingestion of breast milk containing the protein of egg eaten by the lactating mother. The egg white allergy is not significant in the bottle-fed infant unless this food is fed the child early in life. The degree of egg sensitivity can be high and if egg is ingested, violent symptoms could appear, especially urticaria. Milk allergy also can occur early since large amounts of it are consumed alone during the first months of infancy. Those who are extremely sensitive to this food will be made ill by the ingestion of even small amounts. Others may be less allergic, and trouble will not occur until milk has been consumed daily for a while.

Most bottle-fed infants take a very large amount of milk protein in relation to their weight and also their digestive capacities. Therefore, it may be assumed that some of this cannot be completely digested and that it is possible for the products of incomplete digestion when absorbed to cause a vascular reaction in the upper corium. There is a gradual escape of fluid out of the cells with a secondary epidermal involvement.

Some infants who reveal positive skin tests in the form of a wheal, which is an urticarial reaction and not a dermatitis, do not appear to be disturbed by the ingestion of milk. Others who are negative to skin testing are quickly upset by cows' milk. These children, found by clinical trial to be allergic to milk, need help and substitutions must be made in the diet. Other foods which have given positive skin reactions or which have been discovered by elimination diet to be causative agents are cereals, especially wheat, vegetables, meats, and fruits.

The urticarial type of skin test appears to be unimportant. However, the positive wheal response cannot as yet be accepted as insignificant or incorrect. There is too much evidence to prove that the ingestion of food allergens, which have given distinct skin test reactions, cause repeated disturbances in the skin or gastrointestinal tract. Such disturbances may cause irritability with subsequent flare-ups in the eczema or dermatitis. When fresh extracts are employed and the tests are uniformly applied with little trauma, the correlation between positive reactors and clinical reactions becomes better.

Allergic dermatitis and contact dermatitis have been too sharply separated in the past. As the child grows older, the former tends to localize more and more on the neck, the arms below the elbows, and the legs below the knees suggesting possible contact origin. Hospitalization at this stage of the atopic eczema may be beneficial. Environmental allergens such as house dust, feathers, wool, animal danders, clothing dyes, soap, and so forth, may thus be avoided. As a result more emphasis is being placed on the employment of specific therapy with extracts of house dust with or without extracts of other allergens.

As the child grows older, he displays less clinical sensitivity to egg. It may entirely disappear although cutaneous tests may remain positive. This may indicate that children do not absorb the whole protein of the food. Thus more reaches the skin, and no harm results. However, the skin tests with inhalants and contactants become more accurate. Environmental allergens which are inhaled can get into the blood stream and thence to the skin with a flare-up in symptoms. The eczema on the face may heal but that on the extremities remains. A chronic state evolves and there is much trauma. The child becomes high strung and most disturbing to the family who are apt to be rather impatient. This situation has been called neurodermatitis. It is treated less by special diet and topical medication than by keeping the general condition of the individual in the best condition possible and trying to employ some psychotherapy.[8]

Another form of dermatitis found in the infant is atopic erythroderma[9] which occurs less frequently than allergic eczema and begins as a seborrheic dermatitis of the scalp, followed soon by an intertrigo of the neck, axillae, and groin. The condition spreads rapidly and soon the entire surface of the body may be involved. The skin is red and thickened. Varying degrees of edema of the skin and subcutaneous tissue exist during the acute phase and during exacerbations. Vesiculation so characteristic of atopic dermatitis is usually absent. Much scaling is present, which is a striking feature of generalized or disseminated seborrhea. The scales are white and dry. They resemble those of Leiner's disease. In most cases there is pronounced itching with extensive trauma if the child is not properly restrained. Secondary infection can occur with enlargement of the lymph nodes in the occipital, axillary, and inguinal regions. The general condition of the child may not be good.

Infants with atopic erythroderma often have a marked cutaneous reaction to egg white and later in life quite consistently react to other foods especially fish, nuts, and chocolate. The ingestion of egg can cause a violent disturbance in the gastrointestinal tract. Other allergens such as dust, feathers, and animal danders can produce positive skin tests. At first contact with these allergens usually causes little trouble, but respiratory symptoms may occur later.

The disease continues for one to two years with occasional remissions which have no relationship to therapy, but finally the skin begins to clear more and more. However, about that time there are frequent so-called colds or upper respiratory infections. The white blood cell count is elevated, but the increase is chiefly due to eosinophils indicating an allergic situation exists. This is soon confirmed when examination reveals definite evidence of allergic rhinitis. This alone may be present for an indefinite time only to be followed by a chronic cough and finally asthma.

The care of atopic eczema or allergic dermatitis is not too difficult.[10–20] The skin may be cleaned with soap and water, not an oil. Lowila Cake is preferred.

Lotions, creams, and ointments should be mild to moderate in character. A thin layer should be applied many times during the day and several times at night. As often as the infant rubs off the preparations, more must be placed on the areas of eczema. The following have given good results if employed in proper order for the various stages of the disease.

Early period of erythema and papulation

℞ Cetaphil	60 gm., or
℞ Zin-Emul No. 1 (nonoily zinc and starch lotion)	120 "
℞ Calotex (with or without ¼ to ½ per cent phenol)	120 "

Weeping stage of the disease

℞ Burow's solution (liquid aluminum acetate) prepared with Domeboro tablets or powder and used as a continuous moist pack	
℞ Domeboro ointment or hydrosol	60 gm.

Postweeping period when skin is still moist

℞ Bur-tar-gen	60 gm.
℞ Naftacol	60 "

Healing stage of the eczema

℞ Ultar	60 gm.
℞ Kolpix "A"	60 "
℞ Va-Tar "A" or "B"	60 "
℞ Juniper Tar Ointment	60 "

Contact with certain allergens should be avoided. Woolen clothing, blankets, and bedding should not touch the skin of the eczematous infant. Pillows and mattresses stuffed with feathers of any kind must be removed. Cats and dogs should not be permitted near the infant. Dusty things and places must be avoided. All these precautions indicate that the environment of the child with atopic eczema must be kept as clean as possible.[21–24]

Some sedation may be necessary for the mild to moderate degree of itching which is present. This may be accomplished by employing the antihistamines such as Histadyl Syrup, Decapryn Syrup, Phenergan Syrup, or Elixir Benadryl. Occasionally it is best to add ⅛ gr. of phenobarbital to each dram of the antihistamine. The combination works well.

The infant with atopic erythroderma is most difficult to control. The skin is easily irritated and requires gentle care. It may be cleaned with Allercreme Detergent oil, Almay Soapless Detergent, or washed with pHisohex and water. If there is much itching, Almay Sulfonated Oil without or with tar (5 per cent Juniper Tar Ointment) can be employed. Almay Tar Bath also has been tried. It is better than the colloidal baths.

The intense itching of atopic erythroderma interferes greatly with healing. Sometimes cold moist applications temporarily relieve the pruritus. Lotions or creams containing antihistamines are of no value. However, Quotane lotion or ointment has helped. On the other hand, the highly recommended Hydrocortone acetate ointments, 1 per cent and 2.5 per cent, have been disappointing.

All lotions and ointments should contain little petrolatum and the following can be recommended at this time.

Seborrhea of the scalp must be cleared up.

℞ resorcinol 1 or 2 per cent in Aquaphor	60 gm.
℞ Salicylic-sulfur Unguentum	30 "
Dermabase	30 "
℞ Pragmatar	60 "

Soothing and softening creams may help the dry skin.

℞ Polysorb	50 gm.
Distilled water with 2 drops oil of rose	100 cc.
℞ Lamo cream	60 gm.

Pruritus must be controlled.

℞ Menthol	3 gm.
Phenol	6 "
Croleum	120 "
℞ Menthol	3 "
Phenol	6 "
Lubriderm	120 " , or
℞ Zin-Emul No. 2 with menthol and phenol	60 "

Healing can be assisted by some preparations.

℞ Menthol	0.06 gm.
Liquor Carbonis Detergens	3 "
Zinc oxide	3 "
Dermabase	60 "
℞ Vioform 3 per cent cream or ointment without or with ¼ per cent menthol and ½ per cent phenol[25]	60 "
℞ Supertah "5" or "10"	60 "
℞ Kolpix "D"	60 "

Restraints are often required to reduce trauma. Cuffs as illustrated are first considered (figure 1). They prevent the infant from bending the arms at the elbow and scratching the face. Next, it may be necessary to employ further restraints for short periods of time. The arms and legs are then held outstretched by means of wide strips of cloth extending from the wrists and ankles to the bars on the crib. The skin at the wrist and ankle must be well protected with cotton. If the child rubs the face on the bedclothes, a sheet of heavy plastic material can be employed. A piece about 2 ft. square is fastened to the bed under the infant's head by strips of adhesive tape.

Sedation is important. Somnos and Noctec Liquid have helped, but sometimes it is necessary to give the chloral hydrate by rectum in doses of 5 to 10 gr. or even more. The barbiturates may or may not be effective. Nembutal Elixir or Amytal have been used in fairly large doses.

Attention should be given to the diet of the infant with eczema.[26–28] If the child is breast fed, the mother should continue to nurse the infant as long as possible. During this period she may omit egg white from her diet. In addition all foods which cause gastrointestinal distress or urticaria should be avoided. Artificially fed children receive, of course, no eggs and the milk feeding depends on the type of eczema. The infants with allergic dermatitis may be started on boiled evaporated cows' milk, and later changed to goats' milk or Nutramigen. Those with atopic erythroderma may be tried on Non-fat dry milk, Dryco, or Alacta, all of which can be reinforced by the addition of Casec. Later Dalactum can be substituted.

These milk preparations are not always satisfactory, chiefly because a sensitivity to milk casein can easily be found among the children with atopic eczema, and there are also some cases of seborrhea with eczema which do not tolerate cows' milk.[29] As a result, there has been a tendency to substitute vegetable proteins. Most popular is Mull-Soy which is an emulsified concentrate of water, soy flour, soy lecithin, soy oil, sucrose, dextrins-maltose-dextrose, dextrose, calcium phosphate, calcium hydroxide, and salt. The nutritional value closely resembles cows' milk in content of protein, fat, and carbohydrate. The preparation is exceptionally palatable, readily tolerated, and easily digested.

Soy proteins contained in Mull-Soy are recognized for their high biologic value among vegetable proteins. Clinical observations have shown that they provide for normal growth, development, and sound nutrition.[30–34] Recently well-controlled studies confirmed this. No alterations were found in the serum proteins of infants fed soy proteins. None of the children developed hypoproteinemia.[35]

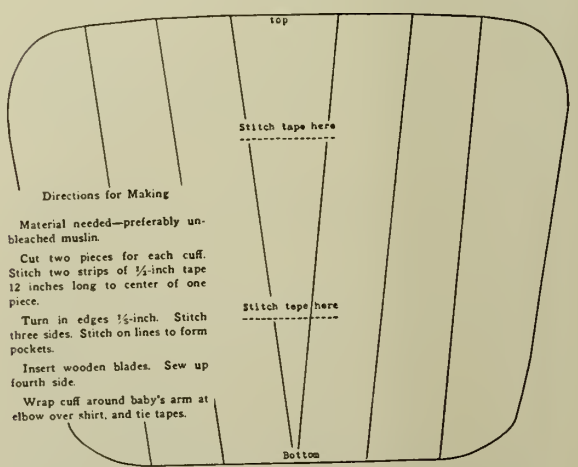

Fig. 1. Pattern for cuffs to be placed on arms of eczematous infants for reducing trauma.

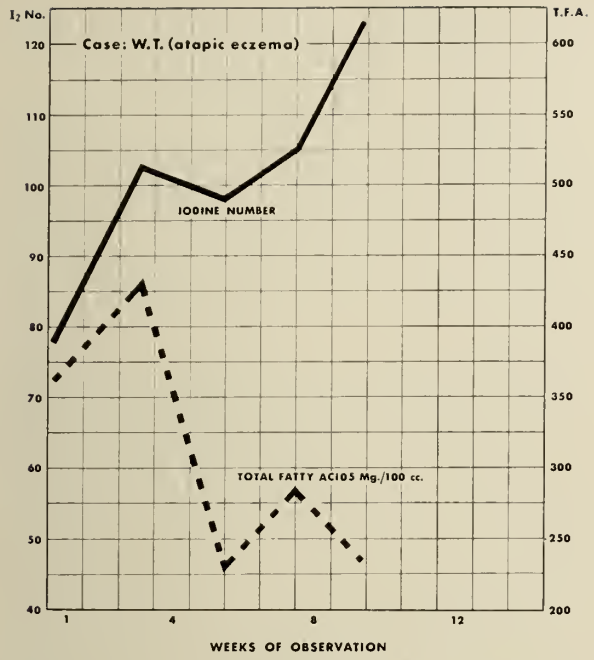

Fig. 2. Case W. T. revealed a definite milk allergy which responded to the soy bean milk with a good rise in the iodine number and a rapid improvement in the eczema.

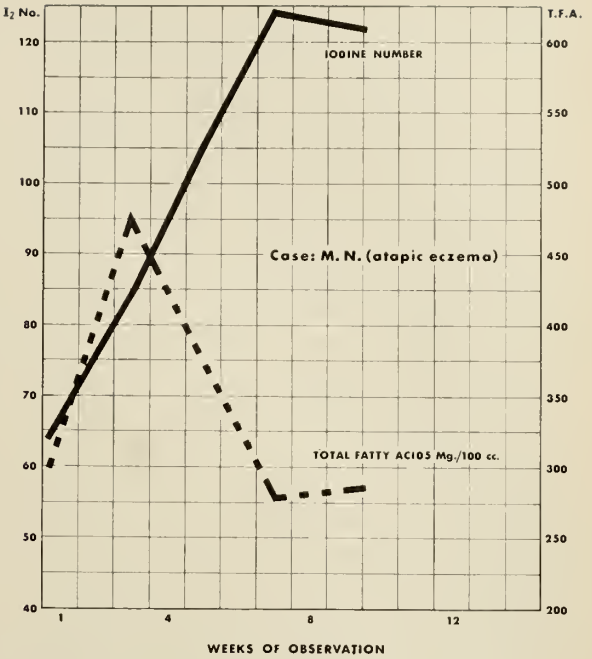

Fig. 3. Case M. N. showed a 3+ reaction to milk and received soy bean milk after which there was an immediate rise in the iodine number and improvement in the condition of the skin.

The fat in Mull-Soy is composed entirely of soy oil, an excellent source of unsaturated fatty acids which have specific biologic functions. Included are three essential acids: namely, linoleic 49.3 per cent, linolenic 2.2 per cent, and arachidonic 0.7 per cent. The degree of unsaturation as measured by the level of iodine absorption is 119 to 135 which is, of course, much higher than iodine number of 26 to 28 for butter fat.

The introduction of a soy bean preparation to an infant's diet should be gradual. Mull-Soy ought to be diluted with 3 parts cooled, boiled water and to this mixture may be added sufficient carbohydrate to increase the caloric value to the desired level. After three to five days, this diluted formula is gradually strengthened over a period of five to seven days by increasing the amount of Mull-Soy and decreasing the water and carbohydrate until a 1:1½ dilution is attained. Next, the child is offered a 1:1 formula and watched for tolerance. About one-third of the infants have large soft stools and occasionally this goes on to frequency of bowel movements. Boiling the formula gently for a few minutes and/or adding a kaolin-pectin mixture often corrects the condition. Less than 2 per cent of the children cannot take soy products. This objection is difficult to remedy and may lead to nausea and vomiting.

The routine use of Mull-Soy in all cases of infantile eczema is not a satisfactory procedure. Some infants appear to improve; others fail to respond. The children who do well are found in many instances to be those allergic to milk either by skin testing or trial diets. However, there are infants with a definite milk sensitivity who are not benefited. On the other hand, some children with no demonstrable milk allergy make good progress.

Previous investigations indicated that soy products not only exerted a favorable influence through substitution therapy but also by means of the high degree of unsaturation of the fatty acids of the soy oil content. Eczematous infants with initial low levels of unsaturated fatty acids of the plasma lipids responded best. Further studies were conducted with three groups of cases: namely, controls, children with allergic dermatitis, and infants with atopic erythroderma.[36–47]

The control group was composed of 28 infants and children ranging in age from three months to two years. None had evidence of allergy. They were receiving either evaporated milk formulas or whole cows' milk along with eggs, cereals, meats, vegetables, and fruits. All were eventually given Mull-Soy in place of milk, and the usual bowel disturbances were encountered with a few instances of difficulty in feeding the soy product. Before the Mull-Soy was started, a blood sample was obtained. After a few weeks

of ingestion of the preparation, the second specimen was taken, to be followed by others collected at approximately three-week intervals. All blood samples were drawn uniformly after a fast of twelve hours. The total fatty acids were obtained by the microgravimetric method of Wilson and Hansen, and Hansen's modification[48] was employed to determine the iodine absorption of the serum fatty acids. These chemical procedures are still too difficult for routine clinical application. Better technics are needed before the significance of essential fatty acids can be completely understood.

The results revealed that the total fatty acid values ranged from 274 to 494 mg. per 100 cc. of serum with iodine absorption numbers between 97 and 143 and an average of 118. After two to three months there was no change. The total fatty acid values then ranged from 272 to 432 mg. per 100 cc. of serum with iodine absorption numbers between 98 and 125 and an average of 114.[49–52] The Mull-Soy was discontinued. During the time the normal children were receiving the soy product, growth and development were most satisfactory.

The second group was composed of 127 infants and children with atopic eczema of the same age range as the controls. All were skin tested or given the trial diets. As a result, 89 were found allergic to eggs, 78 to cows' milk, and 69 to egg and milk. There were also sensitivities to wheat cereals, potatoes and tomatoes, fish, beef, nuts, chicken, chocolate, and citrus fruits. Therefore, the majority of these children were not receiving egg white. Cows' milk had already been replaced in many instances with goats' milk or Nutramigen, and the same infants plus those children allergic to other foods were on elimination diets. After the initial blood samples were collected, Mull-Soy was substituted for the milk formulas. No other changes were made except to omit tar from the topical therapy. The soy product was continued for several months. During this period, the children were closely watched and more samples of blood were obtained periodically. These were analyzed for total fatty acids and iodine absorption numbers. The response to the ingestion of soy bean preparations is best illustrated by a number of selected cases, briefly reviewed as follows.

Case W. T. (figure 2) was definitely allergic to cows' milk. The first iodine absorption value was fairly low. Mull-Soy produced an over-all pronounced rise in the unsaturated fatty acids of the serum so that the iodine number reached 122. The allergic dermatitis rapidly became better.

Case M. N. (figure 3) was more sensitive to cows' milk. The initial iodine absorption value was much below normal. Soy bean milk gave a prompt and steady rise in the unsaturated fatty acids as indicated by the iodine number of 124. The atopic eczema which had been quite extensive showed good improvement.

Case W. M., Jr. (figure 4) was most allergic to cows' milk. Therefore, it was assumed that the introduction of Mull-Soy would certainly be satisfactory, but unfortunately the expected beneficial effect did not occur. The first iodine absorption value was close to lower level of the normal range, and the soy product produced a rise which was not sustained. Therefore, additional soy oil was given in doses to 2 to 3 tsp. with each meal. The iodine number again rose and was associated with some improvement.

Cases T. M. and R. J. (figures 5 and 6) had no demonstrable milk allergy. The initial iodine absorption values were below average. Although it was not necessary to use Mull-Soy in cases of this type, it was thought worth while to try the preparation in order to observe its influence on the unsaturated fatty acids. The first infant eventually responded with a rise in the iodine number and its skin condition became better, while the second child had a fall in the iodine number and little change in the eczema.

It is apparent that the few cases selected to represent the various situations present in group 2 revealed the fact that all children, whether milk sensitive or not, do best when unsaturated fatty acids are at first low and can be elevated by soy products without or with additional soy bean oil. Of course, the results are most striking when the infant who is allergic to milk has a low iodine absorption value, and least striking when no cows' milk allergy exists and the unsat-

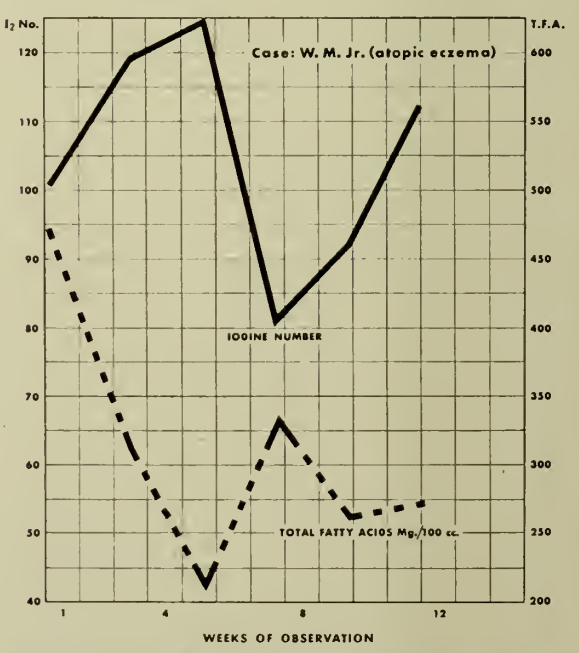

Fig. 4. Case W. M., Jr., revealed a 4+ skin sensitivity to milk and first obtained soy bean milk, later soy oil with no constant elevation of the iodine number. As a result there was not much improvement in the dermatitis.

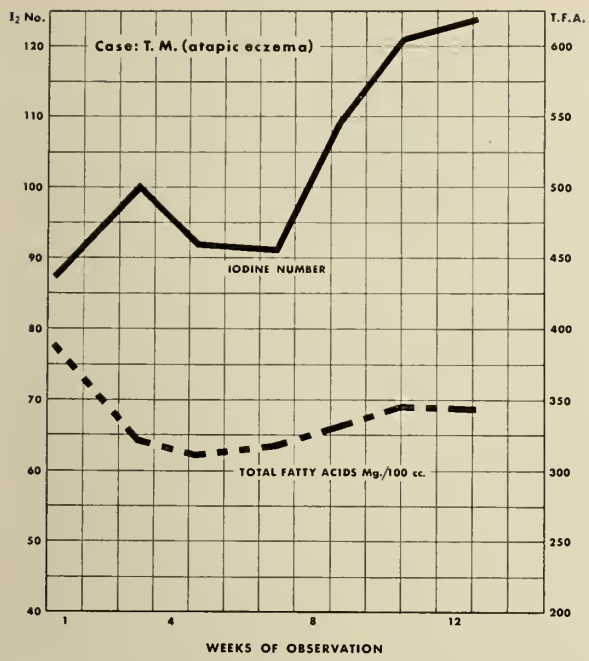

Fig. 5. Case T. M. showed no definite milk allergy but eventually responded to soy bean products with a rise in the iodine number and some improvement in the skin condition.

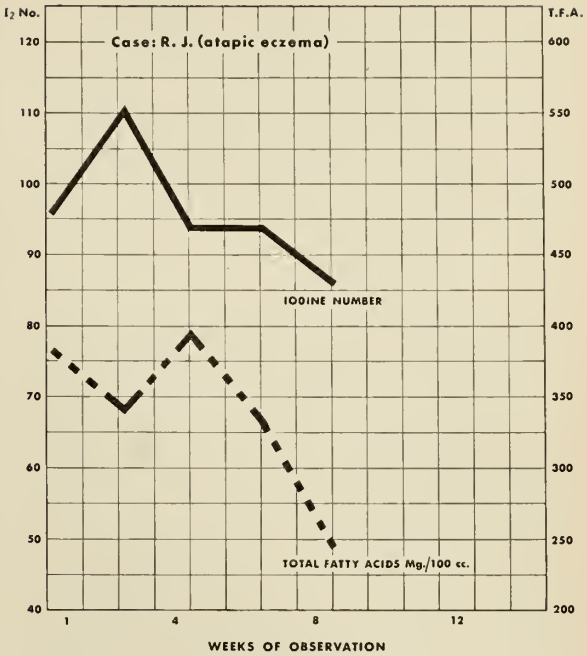

Fig. 6. Case R. J. revealed no milk allergy but received soy bean milk for the entire period of observation with a drop in the iodine number and no improvement in the eczema.

urated fatty acids are practically at a normal level in the blood.

The third group was made up of 36 babies with atopic erythroderma. The majority were referred stubborn cases first seen between the ages of six months and one and one-half years. Cutaneous tests were applied whenever possible or trial diets instituted. There were 29 children sensitive to egg, 14 to cows' milk, and 12 to egg and milk. A few gave positive reactions to other foods, especially fish, nuts, and chocolate. None of the infants were given egg white. About one-third of them were on powdered skimmed milk formulas usually reinforced with carbohydrate or Casec, and the remainder received evaporated cows' milk. Other foods were well tolerated, and, therefore, little use was being made of elimination diets. However, the mothers were instructed to rotate the cereals, meats, vegetables, and fruits, and to avoid fish, nuts, and chocolate. Foods which repeatedly could cause definite flare-ups in symptoms were omitted. If instructions were carefully carried out, little elimination was necessary. Thus the possibility of underfeeding the children was avoided. Mull-Soy was offered regardless of whether the infants were skin sensitive to cows' milk or not. The preparation was not well tolerated. In fact the highest incidence of gastrointestinal disturbances occurred among children with atopic erythroderma. Blood studies to determine the total fatty acids and iodine absorption numbers were made. They revealed little change from the average values as is illustrated by the two cases selected to represent this group and which are as follows.

Case B. C. (figure 7) did not appear to be allergic to milk. The iodine number was within the normal range and ingestion of Mull-Soy for months did not raise it, but instead a fall in value occurred. Meanwhile the infant's skin condition remained the same.

Case J. D. (figure 8) was similar except in this instance the soy product was given along with additional soy bean oil. The unsaturated fatty acids as indicated by the iodine absorption values were sustained at a fairly high level, but the eczema did not improve.

All these observations add up to the fact that there is still no cure for infantile eczema. However, the majority of the cases can be classified as true allergic dermatitis, fewer as the little understood so-called atopic erythroderma, and the remainder as nummular eczema of unknown origin, infectious eczema, and others.

Topical therapy has given the infants with allergic dermatitis some relief. Over half of these children eventually become allergic to cows' milk, and soy bean products are adequate substitutes. Mull-Soy gives the greatest benefit to infants with the lowest level of unsaturated fatty acids in the blood. The soy preparations can be fed for many months during which time, if the iodine absorption values move up into the normal range, most satisfactory clinical improve-

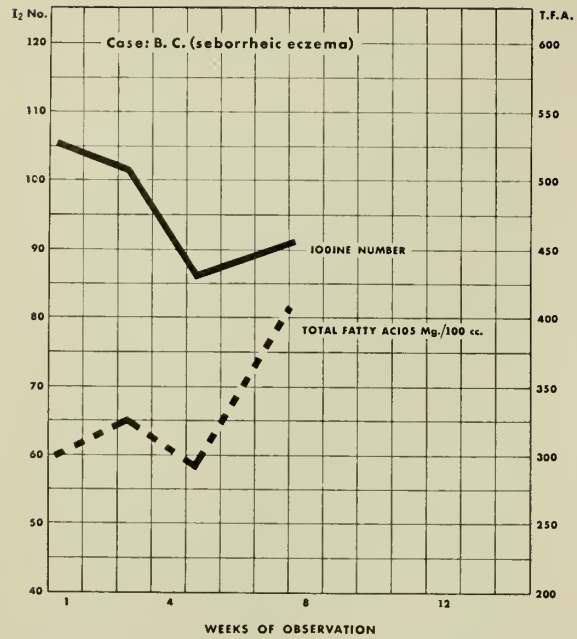

Fig. 7. Case B. C. showed no clinical evidence of milk allergy but obtained soy bean milk with no rise in the iodine number and no change in the condition of the skin.

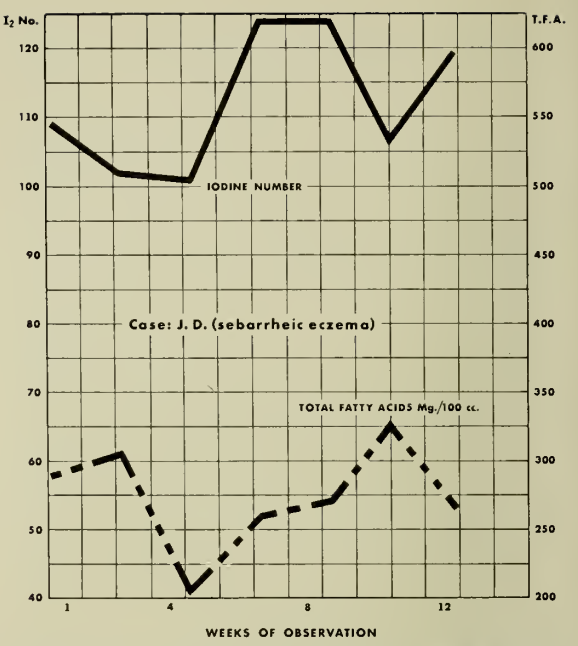

Fig. 8. Case J. D. revealed no milk allergy but received both soy bean milk and soy oil with some elevation in the iodine number. However, the skin condition did not improve.

ment will occur. A few cases even develop a decreased sensitivity to solid foods such as wheat. On the other hand, a similar number fail to respond in any way.

The ingestion of soy products for long periods of time by children already strongly allergic to egg white raises the question of the possible development of soy bean protein sensitivity. So far there is no record of this condition having occurred, probably because the unsplit protein is only slightly absorbed for a short period after feeding is begun and then no longer.

Children with atopic erythroderma are only occasionally satisfactorily controlled by external treatment. These infants are highly skin sensitive to eggs and other foods. Mull-Soy is of little help, since the unsaturated fatty acids are not depressed, and the administration of soy preparations produces no change. Milk, but not eggs, may be given to these children with a variety of solid foods which should be rotated and used in moderation. Since the general health of the infants is most important, vitamins, minerals, and iron ought to be employed. Vi-Penta Drops, Aquasperse, Poly-Vi-Sol or Mulcin, with Zymatinic Drops, Mol-Iron Drops, and Fer-In-Sol are recommended.[52]

Infections must be immediately controlled. Skin lesions may be treated with neomycin cream or ointment; otherwise penicillin, intramuscularly or orally, is indicated. Penicillin causes less trouble in infants with eczema or dermatitis than aureomycin, Terramycin, or Erythromycin.

Occasionally the extreme itching of the skin with trauma due to scratching and the great irritability with lack of appetite place the child in a miserable condition. Therefore, recently ACTH or cortisone has been employed to tide the infant over these bad periods. Cortisone is preferred since it can be taken orally in a syrup, 12.5 mg. per dram. A dose of 1 tsp. may be given every four hours day and night for a total of 75 mg. Since the child usually shows improvement quite rapidly, the total dosage per day should be reduced as soon as possible to between 25 and 50 mg. in order to prevent the appearance of a serious disturbance in mineral metabolism. If *the low dosage* of cortisone permits topical medication and the special diet to be more effective, then its administration can be continued for months provided the following facts concerning ACTH and cortisone are remembered: (1) they cure nothing, (2) they are not a substitution therapy, (3) they reduce resistance to infection, and (4) they can easily lead, if given over long periods of time, to gastrointestinal emergencies even in infants and children.

SUMMARY

1. Two forms of infantile eczema: namely, allergic dermatitis and atopic erythroderma have been differentiated as an aid to treatment.

2. Topical therapy may be carried out for each type in a more or less routine and simple manner.

3. Dietary treatment involves elimination of certain foods with or without replacements. Emphasis has been placed on the substitution of a product containing soy bean protein and oil for infants clinically sensitive to cows' milk.

4. Among children with allergic dermatitis in whom the replacement of milk with the soy bean preparation gave a satisfactory response were some who had additional help from the high content of unsaturated fatty acids in the soy oil.

5. None of the infants with atopic erythroderma in whom soy bean products were used as a substitute revealed any definite benefit.

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Hemiplegia: Treatment in the Acute Phase*

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GENERAL INTEREST in the physical rehabilitation of the hemiplegic patient is comparatively recent. A few years ago the treatment of hemiplegia consisted of supportive care during the early stage. At this time the patient was instructed in a few procedures to be used at home and then dismissed from the hospital and more or less forgotten as it was assumed that nothing specific could be done for him. If some actual recovery of function were to occur, no particular care was considered necessary to hasten the recovery. If no recovery occurred, the condition was considered hopeless and the patient was left to his own and his family's resources. However, physicians interested in rehabilitation have been working to some degree with the hemiplegic patient for at least twenty years. Because these efforts have been rewarding, interest in the problem has quickened recently.

Given a patient with hemiplegia, what procedures might be followed in planning for his care during the early phase of his illness? It is important to answer two questions as soon as possible: namely, what is the nature and extent of the underlying illness and to what extent can the remaining functions be utilized to make the patient more independent? An understanding of the nature and extent of the underlying illness is of importance because hemiplegia may result from a variety of morbid conditions. These include trauma, neoplasm, inflammation, and vascular disease. The cause of the hemiplegia will determine to a large extent the character of the early treatment. In addition, it will influence the prognosis and the goals of therapy. A bullet wound of the brain will accomplish its evil in a brief period, but its residuals will be static. In contrast, a stroke affecting a patient who has malignant hypertension may be only one of a dreary series of events leading to early death.

In any attempt to establish the goals of therapy, the significance of some special symptoms and circumstances must be weighed. Aphasia may make communication with the patient difficult and hinder the process of retraining. A diminution of those sensations having to do with the ability of the person to appreciate the position of an extremity in space may require the substitution of visual control of movements of the affected extremities. Frequent convulsions may endanger the patient in his effort to stand or walk. The mental and emotional state of the patient may have a profound influence on his ability or willingness to enter into the program. Any patient when first faced with the handicap of hemiplegia is to some degree anxious and depressed. If his outlook is especially gloomy, he may have little or no enthusiasm for the arduous task of rehabilitation. Brain damage sufficient to cause hemiplegia may diminish a person's intellectual capacities to such a degree that learning becomes difficult. Often, patients are aware of this limitation and react with increasing feelings of frustration and depression. The behavior of relatives may present a problem if they are oversolicitous and anxious. Their ill-advised efforts to spare the patient may cause him to be fearful of making any vigorous efforts to regain his independence. Since rehabilitation is time consuming, the economic burden of remaining away from home for a long period may present a serious obstacle. This may require the period of training to be shortened to less than the time ordinarily considered advisable.

The conditions just mentioned make the problem of rehabilitation difficult, but some circumstances favor a hopeful outlook. Regardless of the degree of involvement, the outlook for benefit from therapy is better for young patients. This is particularly true of children. In general, these young patients can be expected to become independent from the standpoint of self-care. A large proportion of patients who are hemiplegic will recover some function of the lower extremity. Most of them can learn to walk. A satisfactory return of function in the arm and hand is less frequent, but even the return of slow controlled motion of the elbow and shoulder may allow the patient some use of the extremity.

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Although less may be expected from attempts at rehabilitation in the treatment of elderly patients, it is possible that they can be restored to a certain degree of independence so that only minimal care from the family will be required.

CARE AFTER THE COMMON STROKE

Since the common stroke is the most frequent cause of hemiplegia, the early treatment of this condition will be touched on briefly. If the patient is in stupor, the treatment is essentially the same as that of any stuporous person, which is primarily good nursing care. An adequate airway should be maintained. This may require repeated aspiration of the mouth and pharynx. Administration of a mixture of oxygen and carbon dioxide is advisable if there is any doubt about adequate oxygenation of the blood. Early and adequate evacuation of the bladder and bowel should be arranged. Frequent turning in bed is advisable especially for the aged. The use of side rails or even restraints may be necessary to prevent the patient from harming himself during periods of restlessness and confusion.

The effectiveness of attempts to produce vasodilation is as yet uncertain. Evidence indicates that cerebral vasodilation cannot be brought about to any beneficial degree. In addition, there is some evidence to indicate that if significant vasodilation could be produced it would be harmful rather than beneficial. The subject is too complex to be dealt with in the short time available.

Rehabilitation—Rehabilitation may start while the patient is confined to bed. Some physicians believe that the patient with hemiplegia associated with cardiovascular lesions should remain in bed for a period of four to five weeks. Others are less conservative, and, if symptoms do not progress, they prefer to have the patient become active within a week or ten days. Regardless of whether this period is to be one or six weeks, certain portions of the rehabilitation program should be started within the first week after a vascular lesion. The most common deformities are: (1) stiff and painful shoulder with contraction of pectoralis major muscle, (2) flexion of the elbow with pronation of the forearm, (3) flexion of the wrist and fingers, (4) flexion and external rotation of the hip, (5) flexion of the knee, and (6) equinus deformity of the foot. These deformities can be prevented or minimized by proper position and support of the extremity. Changes of position at regular intervals can correct the tendency toward flexion deformities of the hip and knee. These occur particularly when the patient is lying on his side or as a result of improper use of pillows under the knees. A small pillow under the axilla helps to maintain the shoulder in a position of partial abduction. Cock-up splints or other simple splints may prevent most flexion contractures of the wrist and fingers.

Passive Exercise—As important as the splinting and special supports is the daily use of passive exercises. Exercise in which the joints of the paralyzed extremity are moved through a normal range of motion is important in maintaining full length of muscles and stimulating proprioceptive sensations. This also may encourage the return of function of the muscles if voluntary motion is being reestablished. The passive exercises should be done, preferably, by a physical therapist who moves each joint of the involved extremity through as complete a range of motion as is possible without force. However, a member of the family or a nurse can be instructed to carry out these procedures. If pain and contracture are present, the use of heat and massage may be indicated in addition to passive exercises. If the period of rest in bed is to be longer than two weeks, the patient can be taught to use a simple overhead pulley for exercise of the uninvolved side. A sling may be attached to the paralyzed leg and arm in a manner that will enable him to use the normal arm to exercise passively the involved side. If function returns to any group of muscles in the arm or leg at this stage, reeducation exercises should be started. These are done by careful tugging on the tendons and stimulating the stretch reflex, after which the patient should attempt active voluntary motion of the same muscles. Reeducation of the patient with spastic paralysis is more difficult than that of the patient with flaccid paresis. Massive reflex movements may be utilized in the early stages of training to establish usual patterns of motion. As reflex or spastic voluntary movement becomes more controllable, coordination exercises may be added. First the patient should attempt gross slow movement and as he improves he attempts finer coordination.

During the period of rest in bed the patient can be taught and encouraged to carry out some of the activities essential for self-care, for example, feeding and washing himself by using the uninvolved side. Ability to comb his hair and brush his teeth may be a small step toward independence, yet will provide a definite stimulus to morale. He can learn to correct the position of a paralyzed extremity. By use of his good arm he can help prevent contracture of the involved side by exercising the fingers and shoulder pas-

sively. If there is considerable weakness and if atrophy of disuse has occurred in the nonparalyzed extremities, specific supervised, active, and graded resistive exercises may be prescribed to improve muscular strength and endurance.

If the progress of the patient is rapid during the first few days of his illness, he may be encouraged to sit on the edge of the bed for increasing periods. He may sit in a chair or be assisted to stand at the side of his bed. He should be encouraged to assume more responsibility for self-care.

Occupational therapy should be prescribed to provide further supervised exercises for the paretic hand, as well as diversional activities to encourage the use of normal extremities. Occupational therapy may not need to be supervised by an occupational therapist, but may be worked out by the family or patient, even if it consists of no more than trying to do some simple activity which might lead to self-care, such as buttoning a shirt, turning the pages of a book, reading, or working with puzzles. Reeducation and retraining of muscles which are beginning to function should be increased to the point at which active use of these muscles can be encouraged. However, the patient should not be encouraged to carry out activities with the paralyzed extremity during the day unless care is taken to see that he does them correctly. Otherwise he may increase incoordination and inefficient and incorrect patterns of movement may develop. When the patient is able to sit up for considerable periods without fatigue, he may then begin the more strenuous stages of rehabilitation.

SUMMARY

The importance of recognizing the cause of hemiplegia and estimating the patient's capacity to profit from rehabilitation are the first steps in planning early care. Even during the period of rest in bed after a stroke, rehabilitation may be begun and the patient can be encouraged to try some activities which lead to self-care. Some details of the steps in retraining are discussed.

Diagnosis of nonparalytic poliomyelitis should not be made on the basis of a single examination. Multiple, staged tests of the general condition and activities of the patient are best. Diminished work tolerance in a muscle that is but little involved becomes manifest only after strenuous activity. This condition does not prevail during the acute and early convalescent stages.

Eugene Moskowitz, M.D., and Lawrence I. Kaplan, M.D., of Grasslands Hospital, Valhalla, N. Y., by examinations of 75 patients with noparalytic poliomyelitis, one and one-half to six years after the onset of illness, find that 38.6 per cent have slight weakness in one or more muscles, principally the calf and quadriceps groups. Almost 25 per cent have symptoms referable to the site of weakness. Many have increased general fatigability and emotional disturbances such as irritability, instability, and stuttering. No relation exists between the duration of spasm in the hospital or loss or diminution of tendon reflexes and the eventual onset or site of muscular weakness.

The average hospital stay with nonparalytic poliomyelitis can be significantly reduced provided the patient is free of spasm and has had multiple tests for muscle weakness. When the patient is afebrile and has no muscle spasm or respiratory difficulties, mobilization under supervision has no adverse effect on eventual function.

Eugene Moskowitz and Lawrence I. Kaplan: Follow-up study in seventy-five cases of nonparalytic poliomyelitis. J.A.M.A. 152:1505-1506, 1953.

Evaluation of Control of 70 Cases of Diabetes Mellitus*

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Evaluation of the control of the patient with diabetes mellitus is easily ascertained while that person is under the strict care of a physician, but quite different in the interim between his visits to the physician. It was felt for some time that if a person with diabetes were to have his urine sugar kept negative, with no reaction, that those complications associated with diabetes would be offset. However, several studies have shown that even under ideal control, these complications arise quite frequently. Conversely, if a person attempts an adequate control and after a period of many years shows no evidence of complication, then that person has followed an ideal regime. Dr. Joslin presents a medal to those persons who have had diabetes mellitus for 25 years or more and who, after a thorough examination including x-rays, retinoscopy, and the like, show no evidence of arteriosclerosis or other diabetic complications. The physician must take the word of the patient as to how closely he has followed his diet. It has been our policy to spend much time in discussion with the patient as to his status and outlook, and it was rather surprising to find that in one of Dr. Joslin's 25-year patients who had come under our care, information which she gave us indicated lack of exactness in control. We told her that we knew that she must certainly have gone off her diet at some time. She confessed to us that periodically she would get an extreme craving for candy, buy herself a box of chocolates, give herself an injection of 30 units of regular insulin, and consume the entire box. It was stated previously that she had received the gold medal, 25-year medal, and at the time of our complete examination we found no further evidence of complications.

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This instance, together with the fact that we have dealt primarily with the younger age group who are not too anxious to go through life with an extreme restriction, lead us to spend more and more time with each patient training him to know more about his case of diabetes. During this period of education, we define the necessary limitations that he must follow. In other words, just as a doctor is a good physician only when he knows his limitations, so too the patient is successful only when he recognizes his own disability. As a result of this we have spent many hours with each of the 70 patients described in this paper and with an approach similar to that of the average physician, except that a great deal of time was spent in education rather than in control. We realize that it is impossible for a busy physician to spend so much time with each patient. However, we have received such striking results in cooperation that we felt it worthwhile reporting some of our findings.

At the University of Minnesota the students receive routine examinations, and if they have diabetes at the time of examination, this is listed. If there is sugar at the time of examination found in the urinalysis, then a glucose tolerance test is done and in this way we manage to see each individual who has diabetes known or unknown. In addition we have followed faculty members, but they are not included in this evaluation.

Complete history is taken at the time of referral, including diabetic history, history of illnesses, family history, and, above all, evaluation of the patient's approach to his diabetes. Just as the psychiatric patient is led to know that it is his problem, so too do we throw the situation into the lap of our patient. We inform him what is ideal control, and tell him we would be happy to help him to attain it. If the patient is under the care of another doctor we do not interfere with his control, but we inform the physician that our laboratory procedures are avail-

*The University of Minnesota Health Service.

able and that there is a diet table which may be used in training his patient if it is deemed desirable.

Of the 19,358 students who received complete physical examinations, there were 70 who had diabetes, or 36 per ten thousand. Forty-eight of these were male, 22 were female. This is about the same ratio of male to female as in the University population, that is, two to one. The age span was from 14 years at the University High School to about 40 years in the Graduate School. However, the greatest percentage was between the ages of 17 and 27. Fifty-seven of the 70 patients had diabetes discovered as the result of symptoms suggesting an examination and 13 were found on a routine examination, 11 of whom were discovered at the University of Minnesota.

The history included what previous insulins, diets, and control measures had been instituted, and above all, the present situation in regard to caloric intake, insulin dosage, urine testing and control. In addition we asked about periods of hospitalization and any information pertinent to the control problem, such as emotional factors. In checking the family history we found that there was a positive family history in 33 of the 70 diabetics, and it was positive in both sides

TABLE 1
DIET

	Range in calories	*Median*	*Average*
Initial	1500–4000	2750	2600
Subsequent	1200–3500	2400	2300

of the family in 5 of these. On checking the dietary intake (table 1) the range was found to be 1500 to 4000 calories with a median of 2750 and an average of 2600 calories. On checking insulin dosage (table 2) the range was from no insulin to 135 units with a median of 55 units and an average of 56.4 units. This is a consid-

TABLE 2
INSULIN

	Range in units	*Median*	*Average*
Initial	0–135	55	56.4
Subsequent	0–115	50	51.0

erably less average and median than was expected in the young age group (table 3). The age range was from 17 to 37 years at the time of examination with a median of 21 years and an average of 21.6 years. The youngest was diagnosed at 8 months and the oldest at 35 years, with a median of 13 years and an average of

TABLE 3
AGE

	Range	*Median*	*Average*
Examination at U. of M.	17–37 yrs.	21	21.6
Discovered	8 mo.– 35 yrs.	13	14.9

14.9 years. Seven to 8 years had elapsed between the date of onset and our point of evaluation.

We found the predominant group used a protamine zinc insulin and regular insulin combination mixed in one syringe. Fifty of the 70 were in this category. A complete physical examination in addition to the initial one was undertaken, with particular emphasis on weight, blood pressure, and evidence of arterial-sclerotic or diabetic changes such as in the peripheral arteries or in retinoscopy. Forty-five of the 48 male diabetics were normal weight or underweight, whereas 14 of the 22 female diabetics were overweight (table 5). The blood pressure range was from 116/64 to 146/98 with an average of 122/78. With 140 chosen arbitrarily as an upper limit of systolic and 90 as the upper limit of diastolic pressure, 2 of the 70 patients had abnormal readings – the highest being 146/98. There was no evidence of diabetic change except in 2 patients who had diabetic type leg ulcers, 3 who had cataracts, and 4 who showed retinal changes of the typical diabetic type. The patient with the leg change also had a cataract and retinal change including blindness, and 3 of the remaining were highly uncooperative and had been attempting control over a period of years. The only retinal changes during observation were both in females. One of these had been followed by Dr. Wilder at the Mayo Clinic and had been under good supervision. The other had been followed here for four years with adequate but not ideal control, and recent retinopathy had been discovered. Five patients out of the 48 showed 9 changes of a diabetic type, and 3 of these were minimal.

We then explained in lay terms the causes and findings in diabetes and the necessity for adequate control. Each patient kept a daily record of food ingested, including snacks, in order to determine caloric intake at time of examination. They also kept a chart of urinalyses before each meal and at bedtime, and noted reactions or other subjective sensations they deemed important. In doing this we pointed out the causes for some of the changes in their urinalyses, and explained the actions of the various insulins. We adjusted diet according to weight, activity, and caloric intake, and had the patient see the dietitian for further instruction. In several instances the patients were placed on the diet table, in

TABLE 4
INSULIN

	Regular only	*Protamine zinc only*	*Protamine zinc and regular*	*Globin*	*NPH*	*None*
Initial	1	5	50	4	9	1
Subsequent	0	2	28	3	36	0

TABLE 5
WEIGHT

	Normal		*Over*		*Under*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
Initially	17	6	28	2	3	14
Subsequent	27	12	19	2	2	8

TABLE 6

	CONTROL*			COOPERATION		
	Excellent	*Adequate*	*Poor*	*Excellent*	*Fair*	*Poor*
Initially	21	37	12	26	35	9
Subsequently	40	26	4	44	22	4

*Control: Excellent = 0 to 1+; adequate = 0 to 2+; poor = 3+ to 4+ (or with reactions)

order to learn food values more easily and more adequately. We teach the equivalents in foods rather than accuracy in weighing, because the foods themselves are inaccurate. There was a definite drop in the caloric requirements (table 1), so most patients required about 300 calories less to maintain adequate weight and control.

The insulin was adjusted, and since we had been given NPH Iletyn to use on an experimental basis without charge, many of the patients were anxious to try it — particularly those who were fairly well controlled on a 2 to 1 ratio of regular and protamine zinc insulin. Association showed the insulin requirements had dropped approximately 5 units (table 2) and although the regular protamine combination still was high in a percentage we found that 36 patients were on NPH Iletyn and preferred it — primarily because of the infrequent reactions in late evening and early morning. Two patients, however, returned to the regular protamine zinc combination. Also, since initial action was rather slow, we cut down the dietary intake at breakfast and placed it later in the day, for most of the reactions noted came just before the evening meal. These patients were seen weekly until they were in adequate control, and then every other week, once a month, and finally once a quarter. During each visit considerable discussion was held so that the patient understood what was being done and why. It was interesting to note than 1 of the 2 overweight males and 6 of the 14 overweight female patients lost weight. Conversely, 9 of the underweight males brought their weight up to normal. Here, too, the standards of plus or minus ten per cent of normal weight were used to indicate the limits.

We then attempted to evaluate control and cooperation. We arbitrarily picked excellent control as negative to one plus with no reaction; adequate control as negative to two plus with no reactions or a tendency toward a reaction; and a poor control as three to four plus or with reactions (table 6). Here, too, it was also noted that after a period of discussion and education, control and cooperation increased simultaneously. There were 4 patients who were in poor control, and they too were poor in cooperation. One person was a definite psychopath, and one a psychotic who has since been hospitalized. Those who were poorly adjusted emotionally and who we felt required more than the control of an internist were sent to Mental Hygiene for a period of discussion. There were 11 such cases, all of which improved to a certain degree, although only 9 were considered adequate.

Perhaps the most striking emotional problem was in those who had their diagnosis of diabetes made in younger childhood before they were able to care for themselves and who had become dependent upon parents, particularly mothers, for diet control, insulin dosage, and even the actual injection of insulin. These we found the most difficult to work with. Just as most adolescents feel the conflict of dependency and the seeking of independence in regard to their parents, those with diabetes felt it even more so, and as a result were highly resistive. It took

considerable discussion and mental hygiene to obtain their cooperation, but once it was secured, their control improved, since they were in the high intelligence group. Conversely, those patients who had been found on a routine examination here at the University of Minnesota were very easy to control and learned quickly. No dominance of race or color was noted, nor was the proportion of rural to urban patients any different from that of the general University population.

The patients were invited to bring in their wives or parents to discuss food values with the dietitian or physician, particularly with the thought of such things as hot dishes. This proved a considerable boon to the patient. Our approach was to evaluate the patient thoroughly, spend considerable time educating him as to his personal diabetic problem, and recommend reading of diabetic manuals, such as Wilder, Joslin, or Lily. He was then trained in diet and dietary values, with an effort to have him use the same number of calories daily at about the same hours, but with no restrictions in spans of food. Thus if he wanted some so-called sweet, he could have it if he adjusted for it in his caloric intake. Insulin dosage was likewise adjusted to fit caloric requirements depending upon the weight being sought and the type of insulin used. This was adjusted to the requirements and subjective findings of patients, together with objective observations. All the little hints long known in regard to diabetic control, such as care of feet and toenails, carrying of a card stating that the patient has diabetes, and rotation of insulin injections, were carefully explained to the patients, the majority of whom did not know why each factor was necessary. Thus with adequate cooperation the control improved, weight became closer to normal, diet intake diminished as did insulin requirement, and, in general, the patient had an adequate approach to controlling his own insulin and watching his own diabetes, but recognizing his own limitations.

CONCLUSIONS

Diabetic control is not a simple procedure but requires extensive training and education of the patient. An approach to this is presented. The family history of diabetes in a series of diabetic patients was definite, but not so dominant as it was expected. Diabetic changes and complications were few in number and were checked for every year. Blood pressure readings were normal in all but two instances, these being borderline. Few eye or vascular changes were found. Mental hygiene proved of great value in aiding many of the patients with the so-called diabetic personality. Finally, types and combinations of available insulin are mentioned. We were inclined to be most pleased with the NPH Iletyn insulin, although an adjustment of dietary intake was essential.

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General Management of the Cross-eyed Child*

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THE OPHTHALMOLOGIST often finds it difficult to select a topic for discussion with universal appeal for his nonophthalmologic colleagues. Because the general practitioner and the pediatrician usually encounter children with strabismus before they are seen by the ophthalmologist, it was thought that the first group might be especially interested in this subject.

PSYCHOLOGIC ASPECTS

The cross-eyed child presents problems other than that of the obvious cosmetic deformity and important among these is psychologic difficulty. The child is aware that he is different from his playmates; he is ridiculed by his young friends probably more frequently than his parents realize. The child seldom complains to his parents. Rather, he assumes a somewhat abnormal pattern of behavior and often becomes introverted. He is shy, avoids contact with other youngsters, and hides behind his parents when strangers are present. Less frequently, the reverse is true and the child becomes the terror of the neighborhood. It is gratifying to see the beneficial psychologic effect gained by giving such a youngster a straight pair of eyes. The entire pattern of the child's behavior may change within a few months by his return to ocular normalcy.

NONSURGICAL MANAGEMENT

During the past several years a deeper appreciation has evolved concerning the role played by nonsurgical management of strabismus and its complications. It is this phase of the problem which I should particularly like to discuss.

Diagnosis of Strabismus — Coordination of binocular function of the two eyes usually is well established by the time a child has reached the end of his first year. This age varies, just as does the age at which a child gets his first tooth or learns to walk. Certainly by the time the child is fifteen months old his eyes should be constantly straight. Diagnosis of clinically significant strabismus is possible in a child less than one year old, for the intermittent type of incoordination of the eyes seen frequently in normal infants should be present only occasionally. When incoordination does occur, the child is usually tired, hungry, or ill. These same conditions will accentuate strabismus in a cross-eyed child, but even when he is rested, healthy, and well fed, some lack of parallelism persists. This constant lack of coordination makes the diagnosis evident.

Two conditions frequently complicate the diagnosis of strabismus at an early age. When the angle of strabismus is slight, the eyes may appear straight to the parents and often to the physician. Many times this condition is impossible to recognize until the child is old enough to cooperate in some eye-testing procedures. The second condition, and one which is much more frequently encountered, is apparent strabismus in a child who has normal eyes. This false strabismus is caused by epicanthus or pronounced underdevelopment of the bridge of the nose. The inner canthi are obscured by folds of skin which cover much of the normally exposed conjunctiva and sclera located medially to the cornea. These youngsters appear to have crossed eyes, but performance of the cover test or observation of the corneal reflexes discloses that the eyes are straight. These children frequently are referred to the ophthalmologist who can inform the parents that the strabismus will disappear as soon as the child grows a bit more of a nose. Often the true situation can be demonstrated dramatically to the parents by elevation of the fairly lax skin over the bridge of the nose by the physician's fingers. As the epicanthal folds are thus obliterated, the apparent strabismus vanishes.

Probably this latter type of case has led to the erroneous opinion held by many today that

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a child will outgrow strabismus. There are rare cases of accommodative strabismus in which the eyes become straight without treatment. Often, however, the child or young adult who does outgrow strabismus has greatly reduced vision in the eye which previously squinted. Thus he has at best only a cosmetic recovery and not a functional one.

Prevention of Blindness — Ophthalmologists have a vital interest in the functional cure of strabismus. This functional cure can be accomplished in the majority of cases, and thus the nonsurgical phase of treatment is extremely important. Attainment of functional cure is one of the most fruitful aspects of preventive medicine; no other single factor is any more important in the prevention of blindness.

Blindness is usually thought of as involving both eyes, but monocular blindness is also important. As our mechanized civilization progresses, more and more occupations demand good vision in both eyes. Monocular blindness as a result of long disuse of the involved eye can be prevented in almost every case of strabismus by early diagnosis and proper treatment. When one eye is prevented from developing normal vision throughout a person's early years, that person probably will go through life as a one-eyed individual.

Constant strabismus is the most important agent which prevents development of normal vision, and vision is an acquired skill, not hereditary. Normal vision usually can be established if a squinting eye is forced into use by occlusion of the sound eye before the patient is about eight years old. The earlier in life this treatment is begun, the more rapid is establishment of normal vision and the higher is the incidence of eyes that will respond properly. If treatment is postponed until the patient is eight years of age or more, the incidence of good results falls off sharply.

Ocular occlusion of this type, to be effective, must be constant and total. The sound eye must be covered during all the waking hours of the child's life until vision of the squinting eye equals that of the good eye. This improvement of vision, or, more accurately, establishment of vision, may take place within a period of several weeks or, at most, a few months. It is most gratifying to watch these youngsters improve from an inability to see the large E on the test chart to a visual acuity of 20/20. Ability to see only the large E on the test chart is equal to visual acuity of 20/200 and represents occupational blindness. The possibility of improving vision beyond the limit of this latter point by treatment is why I consider that this part of ophthalmology — the prevention of occupational blindness — truly belongs to preventive medicine.

Orthoptics — Other phases of nonsurgical treatment of strabismus exist in addition to occlusion. Chief among these is orthoptics. Training of the binocular function, termed fusion, belongs to this fairly new branch of the visual sciences. Training in fusion has been extremely valuable in augmenting the percentage of functional cures of strabismus, because fusion makes the important difference between eyes that are simply cosmetically straight and those that are not only straight but that work together as a team.

The patient with strabismus may have a repressed form of fusion. In this instance, if the eyes are straightened surgically, fusion may become manifest and a functional cure results. Too often, however, fusion is lacking entirely or is suppressed to the point at which it is merely rudimentary. Properly administered orthoptics for these latter patients, who constitute by far the majority, may allow development of fusion when it is lacking and may increase greatly the amplitude of fusion for those patients in whom this faculty is poorly developed.

Some cases can be corrected by orthoptic training alone. These are usually patients with a fairly small angle of strabismus in whom fusion can be awakened and made to function to hold the eyes straight.

There is no definite program of orthoptics for all cases; each patient requires individualized treatment. Also, there is no specific time when orthoptics is most effective. Many ophthalmologists use orthoptics preoperatively; others use orthoptics only after operation on the ocular muscles has been performed. In still other instances, treatment both before and after operation is necessary.

Refractive Errors — Proper correction of any refractive error also is important in the treatment of strabismus. The exact basic etiology of convergent strabismus in children is still not well understood but at least the role of the accommodative factor can be measured and corrected. Strabismus is purely accommodative in some instances. This type seems entirely related to the fact that the child concerned is abnormally farsighted. Because he is farsighted he must use his accommodative mechanism to excess if he is to see clearly. Normally, the accommodative mechanism works hand in hand with the con-

vergence mechanism, and a certain stimulus to accommodate is accompanied by a similar response of the convergence mechanism. In the farsighted child with a poorly developed fusion mechanism, the excessive demand on accommodation is observed as an excessive exercise of convergence. If the farsightedness in these accommodative cases is corrected by use of glasses, the need for excessive accommodation with its reflexly related convergence is abolished. Thus, in some cases strabismus can be corrected by glasses alone.

SURGICAL MANAGEMENT

More often than not, however, surgical procedures are necessary in addition to glasses and orthoptic training. Some accommodative element is present in the great majority of cases of strabismus, and thus glasses partially may correct the condition. Orthoptic treatment is also needed, because fusion is imperfectly developed in most cases. Otherwise, strabismus probably would not have developed.

Little change has been noted in the surgical management of the usual horizontal type of strabismus since the time of Jameson. In 1922, he instigated wide acceptance of the concept of scleral fixation of the ocular muscles, and since then utilization of free tenotomy of the horizontal rectus muscles has practically vanished. The choice of operation in any individual case is still open to argument, probably because often there are two or more methods by which the same degree of correction may be attained. There is a trend, however, toward attempting optimal correction in one operation rather than performing operations on muscles in stages because of fear of overcorrection. If two eyes have developed fusion either spontaneously or through orthoptics, it is important that the surgeon place the eyes in such position that this fusion may be used. Partial correction fails because it does not produce parallelism and does not allow the binocular mechanism to function.

DIVERGENT STRABISMUS

The preceding discussion has dealt with the cross-eyed child. Similar problems exist in the child with divergent strabismus, but this type of case is more infrequent than is the convergent variety. Ordinarily, divergent strabismus begins in children as an intermittent or periodic wandering out of one eye. Recognition of this early intermittent period is most important because treatment at this time usually produces excellent results. Treatment that is delayed so long that a permanent, cosmetically disfiguring, divergent strabismus is reached often produces results which are disappointing in regard not only to function but often to appearance as well. Second and third operations are not unusual, for divergent strabismus is notoriously difficult to correct. This condition usually appears later in childhood than does convergent strabismus, and most patients with the divergent type have developed good vision and fusion. The eyes must be put in proper position to allow maintenance of these valuable attributes. Surgical procedures that correct only part of the deviation are out of place, for if parallelism is not achieved the mechanism of fusion cannot take over and function normally. Usually, the operation of recession on both external rectus muscles is necessary.

OTHER TYPES OF STRABISMUS

The more unusual types of strabismus that occur are of interest only to the ophthalmologist. These usually are the vertical or combined horizontal-vertical variety. The surgeon approaches operations on the vertically acting ocular muscles with much less timidity than formerly, and satisfactory results usually can be obtained.

May I close with a plea for early recognition of and treatment for the child with convergent or divergent strabismus, so that in later life the eyes not only possess a parallel appearance but also function as a normal binocular team.

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.*

Case Report of Anthrax Acquired in a College Research Laboratory

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We are interested in reporting this case because of its rarity in modern times and because of the unusual sequence of events which made this infection possible.

Anthrax is an ancient disease which was quite prevalent during the Middle Ages among those coming in contact with domestic animals and the hair and hides from such animals. History indicates that the mode of transmission between animals and humans was recognized at times when superstitions concerning diseases were at their height, making this disease unusual in this respect.

Early treatments were varied and unscientific until the development of wide surgical excision of the lesion. This mode of treatment reduced the mortality but it still remained a serious infection. Later the production of an antitoxin further reduced the mortality rate and additional advances have recently been accomplished in the treatment of this disease by the introduction of antibiotics so that in our present century anthrax produces a very low mortality.

CASE REPORT

On March 3, 1953, a graduate student in bacteriology noted a small crust formation just above the middle of his left eyebrow. He attached no importance to this and forgot about it until the next morning, March 4, when he noticed that the crust had increased in size and had a slight local swelling at its center (figure 1). This finding seemed unusual to him, but inasmuch as he felt normal he proceeded with his day's duties without further consideration. On March 5, upon arising, he noticed a pronounced swelling limited to the left forehead and also some swollen glands just anterior to the left ear and in the left side of his neck.

Fig. 1. Small crust formation above left eyebrow.

These findings concerned him and he reported to a staff physician in the college health service where a clinical diagnosis of anthrax was made and a culture taken on blood agar. At this visit he received a 700,000-unit dose of penicillin.

On March 6 the culture was reported as follows: "gram positive spore forming rods producing no hemolysis; typical anthrax morphology and colony characteristics." Clinically the swelling continued to be pronounced in the left forehead and the lymphatic involvement became greater so that he was given another 700,000 units of penicillin and sent to the college infirmary in the afternoon. On admission his physical examination was entirely negative except for the findings described above. His body tem-

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perature was 102° with a pulse rate of 108 and a respiration of 20. At this time his penicillin was changed to 600,000 units twice a day.

On March 7 the patient appeared to be very toxic and drowsy and complained of severe headache. There was no evidence of confusion or irrational displays. Locally the swelling had increased so that the left eye was partially closed. The central portion of the lesion above the eyebrow was black and depressed and slightly larger than the end of a pencil eraser. About it in the area previously slightly vesiculated were radiating discolored spots of dark necrosis in the periphery. This is the so-called "satellite phenomena." On this date his fever had disappeared and his pulse had returned to normal. These were the only encouraging findings since all other clinical processes seemed to be progressing. Also on this date the laboratory reported that his sedimentation rate was 11 mm. per hour, his hemoglobin 97 per cent with 5,750,000 red blood count and 11,400 white blood count. His differential was simply reported as 60 per cent segments and 40 per cent lymphocytes. Urinalysis was negative.

On March 9 swelling had increased with edema under both eyes. Vesiculation and soft necrosis about the periphery of the lesion had increased. The patient's chief complaint was of severe persistent headache. Attempts to use hot, wet fomentations as advised by the anthrax team of the Warfare Bacteriology Group at Camp Dietrich, Frederick, Maryland, seemed to increase this patient's headaches to such an extent that he objected to the treatment and this was discontinued. Because his clinical progress did not seem to be arrested, several of the medical staff in consultation agreed that ½ gm. of streptomycin twice a day should be incorporated in this patient's treatment regime. Our decision in this respect was influenced by the fact that early in the disease antibiotic sensitivity tests indicated that the culture from this man's lesion was more sensitive to streptomycin than to penicillin. At the time of our evening visit to this patient, we felt that the facial swelling probably had started to diminish.

On March 10 the swelling had definitely decreased so that the right eye was now free of edema. The local lesion had not changed in appearance except that it seemed to be drier and harder and a very slight exudate was noted. For the first time the patient complained less of headache on this date.

It was now decided that the results of another culture would be useful and such was performed in the afternoon. Because of the presence of a slight exudate, hot packs were applied again, but, as previously, the headache increased so that they were not continued. During the past twenty-four to forty-eight hours, in addition to headache, the patient also complained of generalized aches and pains particularly in the lower thoracic and lumbar regions and in his leg muscles. These symptoms apparently annoyed him sufficiently to discuss with the medical staff the possibility that he might also be suffering from influenza which was somewhat epidemic in our area at this time. These symptoms were, of course, regarded by us as part of the general toxic picture.

When the anthrax lesion began to subside, the clinical improvement was very rapid and pronounced, so that, on March 11, all swelling of the face was essentially gone. Lymphatic gland involvement was minimal and the local lesion area had returned to normal in its periphery and the central black necrotic region was extremely hard and dry. The intensity of the headache had diminished and the generalized aches and pains had practically disappeared. The twenty-four-hour reading on the culture made on the previous day was reported sterile.

This man's mental retardation and drowsiness had by now disappeared. His temperature had remained normal since 9:00 A.M. on March 7.

On March 12 his face was no longer swollen and only one lymph node anterior to the ear remained congested and tender to the touch. The local lesion was reduced to the hard, dry, black characteristic finding so long identified with anthrax. The patient's sole complaint continued to be headache but this symptom was intermittent and confined to the basal area. Because of improvement he was permitted out of bed for short periods on this date.

By March 13 the patient felt so well that he insisted upon being discharged and left the infirmary with instructions to report to the health service daily until final dismissal.

DISCUSSION

In answer to our inquiry, the American Medical Association office reported to us March 24, 1953, that "at least 30 instances of laboratory-acquired anthrax have been recognized in the United States as disclosed by survey made in 1950. The majority of these occurred in one large laboratory engaged in specialized studies and have been described in the literature. Most of the 30 infections were cutaneous and only one was fatal. The suspicion that one infection was acquired by handling stained smears was supported by demonstrating viable bacilli on such smears."

As soon as the diagnosis of anthrax was made, the head of the department of bacteriology at Penn State contacted Dr. Sutton of the anthrax team of the Warfare Bacteriology Group at Camp Dietrich, Frederick, Maryland. This team reported that they were accustomed to treating anthrax by the administration of 1,000,000 units of penicillin daily for six days. In this instance we elected to use 600,000 twice a day. They also advised the use of warm, wet sterile packs when there was evidence of necrotic breakdown in the local lesion.

This team also advised 3 gm. of aureomycin daily in 500-mg. dosages every four hours in the event of penicillin sensitivity. This variation was not found to be necessary in treating this case.

The patient reported to us that he felt that the probable time of infection was on Wednesday or

Thursday, February 25 or 26, with a second possibility on Monday, March 2. We surmised that on some of these dates viable organisms entered the skin just above his left eye by transmission from hands or fingernails to this area.

An interesting sidelight in this particular instance is furnished by the following observation. The research project in which the patient was engaged was being performed by use of avirulent anthrax organisms obtained from the Army Medical School, Walter Reed Hospital, Washington, D. C. After the development of this case of anthrax, this specimen was suspected and immediate animal inoculation was done to determine its possible virulence. This animal testing proved the nonvirulence of the original culture immediately under suspicion. Initially, in 1950, guinea pig inoculation proved this culture nonpathogenic. However, in the course of proceeding with this research problem, it was necessary to "heat shock" these nonvirulent organisms. This laboratory procedure consisted of exposures of anthrax spores suspended in 0.85 per cent sodium chloride solution to 85° C. for ten to thirty minutes. This "heat shock" is a standard procedure used to select for more vigorous cultures but there is no direct correlation between growth on agar plates and pathogenicity. Such pathogenicity is usually extremely difficult to restore to an avirulent strain of any organism. An inoculation of mice from the "heat shock" portion of this supposedly avirulent culture proved these organisms to be deadly inasmuch as these animals died within eighteen hours.

Thus, the source of this infection seemed without any doubt to be from an avirulent culture of anthrax which became extremely virulent after "heat shock" application which was necessary in the pursuit of this problem.

CONCLUSION

A case of laboratory-acquired anthrax is reported from the bacteriological research division at the Pennsylvania State College. This patient recovered completely and promptly by use of modern antibiotics. The anthrax lesion has locally at this time completely separated, leaving an almost normal appearing skin at the site of original invasion.

This patient had no complications and has continued with his postgraduate work in a normal manner since his discharge from the college infirmary.

The fact that this case of anthrax was acquired from a nonvirulent culture, activated by a "heat shock" procedure performed in the course of this research problem, is to our knowledge an unusual and extremely important finding.

The total dosage of antibiotics used in the treatment of this patient was 9,800,000 units of penicillin plus 4½ gm. of dihydrostreptomycin.

Toxic hypervitaminosis D should be suspected when unusual symptoms develop in a patient receiving vitamin D. Usually the intoxication develops only after amounts of the vitamin in excess of 100,000 I.U. have been taken daily for several months, but lower doses may be toxic. If the vitamin intake is not limited, the condition can be fatal.

Indications of poisoning include nausea and vomiting, diarrhea, fatigue, weight loss, headache, paresthesias, depression, normocytic normochromic anemia, urinary frequency, nocturia, albuminuria, hematuria, progressive loss in urinary concentrating power, rise in nonprotein nitrogen, elevated serum calcium and phosphorus, with normal alkaline phosphatase, and roentgen signs of diffuse demineralization of bones or periarticular calcification. These symptoms and signs, emphasizes Albert Weinstein, M.D., of Vanderbilt University, Nashville, can appear in any order or combination.

Although many of these conditions also occur with primary hyperparathyroidism, the serum phosphorus and alkaline phosphatase levels in hypervitaminosis D are normal or but slightly elevated, whereas in the endocrine disorder the serum phosphorus is usually low in association with pronounced elevation of the alkaline phosphatase.

Hypervitaminosis D should be prevented but, once developed, must not be overlooked. If the vitamin is discontinued, renal failure and irritation will usually disappear and the metastatic calcification in the kidneys and soft tissue will generally reabsorb.

Albert Weinstein: Vitamin-D poisoning. J. Tennessee State M. A. 46:140-142, 1953.

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.*

Observations on the Anatomy and Development of the Lungs*

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It is of interest that the gross units of the bronchial tree were first worked out by a pathologist – Dr. William Ewart of Brompton Hospital.[11] Seeking a more accurate method of establishing the site of "lung cavities," he divided the lungs into nine districts on the basis of the largest bronchi arising near the hilum of the lung. In so doing he took issue with the Swiss anatomist Aeby[1] to whom we are indebted for the first comprehensive account of the bronchial tree in mammals. Aeby described the tree as consisting of right and left axial trunks which, distal to the eparterial bronchus, give off alternating dorsal and ventral branches. Ewart pointed out that while this might be true in quadrupeds, the human pattern is quite different due largely to the shape of the human thorax. In man the lungs are compressed from front to back and limited inferiorly by the heart. Hence the human bronchial tree is characterized by a more radial pattern.

Ewart, however, was far ahead of his time. The doctrine of the stem bronchus prevailed until the 1930's when Glass,[16] a surgical resident at the Mt. Sinai Hospital in New York, developed *de novo* the idea of "bronchopulmonary segments," and Nelson,[19] a young thoracic surgeon of Brompton Hospital, revived the work of Ewart. Now through the recent, more comprehensive studies of Foster-Carter[13] and of Brock,[7] again of Brompton Hospital, and of Jackson and Huber,[15] in this country, the concept of these bronchopulmonary segments has become the accepted concept in both anatomic and clinical literature.

At Minnesota, during the last eight years, my colleagues and I have been engaged in analyzing the variations of the segmental bronchi and related pulmonary vessels. Two human lungs are seldom alike. When one segment at a time is viewed in a series of lungs, a characteristic can be recognized, that is, a prevailing pattern for that segment as well as certain characteristic deviations from this pattern. The latter are most frequently due to the displacement of a subsegmental bronchus – a key point recognized by Huntington[14] and responsible for his theory that the lungs of mammals are plastic organs arising in response to respiratory needs and, therefore, not to be arranged in any derivative order.

Many of the deviations noted above have been summarized in the brief article of 1949,[3] and it is hoped to present them all soon in book form. At this time I would like to limit myself to three examples. Prevailingly, the short right upper lobe bronchus trifurcates into apical, anterior, and posterior segmental bronchi (figure 1). These are referred to, respectively, as B^1, B^2, and B^3. Each in turn has two major branches – B^1a and B^1b, B^2a and B^2b, B^3a and B^3b. However, in 16 per cent of 50 specimens,[5] B^3 was observed to "split" in such a way that B^3a arises from a short common stem with B^1, or one of its branches, while B^3b arises in common with B^2. In such specimens the lobar tree has a "quadrivial pattern," and the lobe itself consists of *four* rather than three segments.

The key to variations of the left upper lobe[4] is the "splitting" of the anterior segment, B^2. Usually, the lower of the two anterior bronchi arises from a position intermediate between upper and lingular divisions, thus bringing about a trifurcation of the upper lobe bronchus and the substitution of five for four segments. This deviation from the normal pattern was found in 27 per cent of 100 specimens.

The third example[12] is based upon our study of the medial basal segment of the right lung, B^7, the

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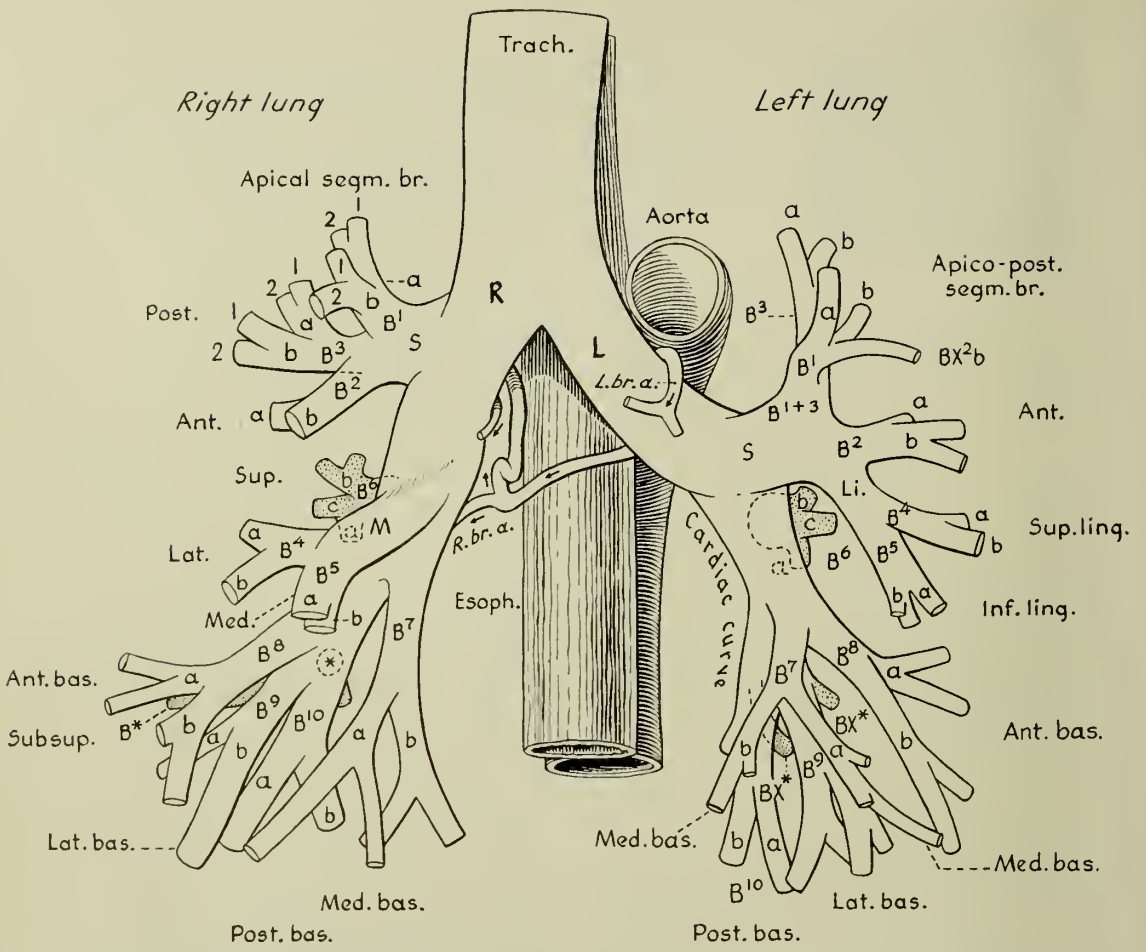

Fig. 1. Anterior view of bronchial tree, showing prevailing modes of branching of segmental bronchi. (From Dis. Chest, 1949). S, M, superior and middle lobe bronchi of right lung; S d, L d, superior and lingular divisions of left upper lobe bronchus; B°, BX°, suhsuperior bronchi; B^1, B^2, and so forth, apical and anterior segmental bronchi and so on; a, b, their principal rami.

one which forms a separate lobe in quadrupeds and frequently becomes separated off in man by an accessory fissure. As in the other segments, its bronchus divides into two main branches, B^7a and B^7b. In addition to two normal types – which vary only in respect to whether the bronchus distributes to both anterior and paravertebral surfaces of the lobe (34 per cent) or merely to the anterior surface (22 per cent)—there are two strikingly different patterns. In type 3, 24 per cent of 50 specimens, the two branches of B^7 surround instead of pass anterior to the basal trunk of the inferior pulmonary vein. This makes surgical resection of the segment hazardous. In type 4, 20 per cent, B^7 is absent as such. That is, the bronchoscopist would find no orifice for the medial basal bronchus. Its two branches, however, are present but are displaced in such a way that B^7a arises from the anterior basal bronchus B^8, and B^7b from a subsuperior bronchus, B°, or the posterior basal bronchus, B^{10}. In viewing such anomalies as those illustrated above, it is inevitable that one should ask, "When, how, and why do such variations arise in development?"

THE EARLY DEVELOPMENT OF THE SEGMENTS

This section is based upon an unpublished series of dissections and wax models of young human embryos prepared by Professor L. J. Wells of the Minnesota department of anatomy. The material covers Streeter's Horizons XVII, XVIII, and XIX, consisting of embryos of approximately the thirty-fourth to the fortieth day, ovulation age, and ranging in crown-rump length from 10 to 20 mm. This is the period in which the segmental buds and their principal subdivisions arise.

Before the lungs were sectioned they were exposed in situ under the dissecting microscope. Two points of special interest were observed. First, the lungs and pleural sacs do not fill the thoracic cage. Hence it would seem that the segments are not competing for thoracic space. Second, the surfaces of the lungs are lobulated. In Horizon XVIII the lobules are

large and delimit segments. In Horizon XIX the lobules are more numerous, give the illusion of being smaller, and usually delimit subsegments.

Wax reconstructions of the developing bronchial trees reveal many of the variations found in the adult lungs, such, for example, as the four types of the medial basal segment described above. Presumably, all such variations develop not later than the stage represented by Horizon XIX. Contrary to the usual experience, the adult patterns must be known before the embryonic structures can be identified, for the bronchial buds often develop in different sequence in different embryos and from displaced sites on bronchial trees of embryos of the same age. In fact, no 2 of the 9 modelled specimens were found to have exactly the same pattern. From this it might be inferred that the variations have a genetic origin. Yet, even this interpretation must be qualified. For a study of Ando's 36 pairs of dissected fetal lungs,[2] taken from identical twins, reveals the fact that the bronchial pattern may vary even in twins arising from one fertilized ovum. Accordingly, it appears that somatic factors also play a role in the formation of the developing tree.

PREPARATION OF FETAL LUNG FOR RESPIRATION

After the segmental bronchi have appeared, the bronchial tree continues to divide, branching dichotomously according to Broman,[8,9] although the 2 branches may be of unequal length. At birth, he counted 18 generations in the middle lobe, including the branches having alveoli. Similarly, Palmer[20] counted 17 generations in the right upper lobe bronchus of a 152-mm. embryo of the nineteenth week, crown-rump length and menstrual age. No additional generations had formed by the twenty-first week, 170-mm. embryo.[21] At this time, generations 1 to 7 were lined by pseudostratified epithelium with superficial ciliated cells, generations 8 to 10 by simple columnar ciliated epithelium, and generations 11 to 17 by cuboidal epithelium. The last 5 were considered to be the immature respiratory portion, since they were only partially covered by light staining cuboidal epithelium. In a somewhat older fetus, 187 mm., the terminal or 17th bronchial generation was described as made up of blind, epithelial-lined end pouches, but in generations 14 to 16 distinct changes had occurred. The epithelium was no longer intact; nude capillary loops bulged into the lumen, adjacent loops being separated sometimes by as few as 4 cuboidal cells. No evidence of the death of the epithelial cells could be found.

The same year, 1936, Dubreuil, LaCoste, and Raymond[10] outlined three stages of differentiation: (1) a *glandular period,* in which the bronchial divisions are established but in which respiration is potentially impossible; (2) a *canalicular period,* from the beginning of the seventh month of gestation to term, a viable stage in which the respiratory portion becomes delineated and vascularized; and (3) an *alveolar period,* in the few weeks after birth, in which the definitive alveoli are differentiated. However, it has remained for Loosli and Potter[18] of the University of Chicago department of medicine to demonstrate the histologic details of these processes in a superbly prepared series of fetal lungs stained with Mallory-azan, or orcein, and ranging in age from three and one-half months to term and beyond that into childhood.

Much of this material was presented at the meeting of the American Association of Anatomists in 1951, and through the generosity and courtesy of these authors I am privileged to discuss their preparations of the fetal lung in advance of final publication.

While accepting the three periods of the French investigators, Loosli and Potter have advanced the time limits by placing the canalicular period from the fourth to the sixth month and the alveolar period from the seventh month to term.

In the glandular period the peripheral bronchi are characterized by a columnar epithelium that is surrounded by a basement membrane, staining blue with Mallory-azan, in which a capillary network is growing.

In the canalicular period the peripheral portion of the bronchial tree becomes less well seen — the terminal air spaces consisting of long channels with pale staining nuclei. This change is attributed to pronounced increase in the growth of interstitial tissue. Early in the period these channels are lined by cuboidal cells, but under the epithelium the "blue" connective tissue fibrils are now spaced at intervals. It is at these points that capillaries first protrude into the lumen, pushing the connective tissue fibrils ahead of them to separate the epithelial cells. Such vascular outcroppings form the tissue which eventually gives rise to the septal wall of the alveolus. By the sixth month no clear-cut connective tissue remains under the epithelial cells, nor are alveoli present. Yet the capillaries that protrude into the lumen are sufficient in number to sustain life for several hours.

In the alveolar period the free ends of the future alveolar septa are tipped by capillary loops, although the basal portions are still lined with cuboidal epithelial cells. As term approaches the vascular septa have protruded far enough into the lumen to delimit shallow alveoli. The alveolar walls are held stationary by elastic fibrils in the septa which encircle the orifices of the alveoli. These are especially prominent at the free ends of the septa where they have been slowly increasing since the fourth month. Meanwhile the areas between the bases of the septa continue to evaginate and enlarge. By this time the epithelial cells have become infrequent. In short, the principal factor in the formation of the alveoli seems to be the spaced invasion of the elongating air channels by capillary loops and the associated interstitial tissue.

After birth the peripheral portion of the lung continues to grow at a tremendous rate. Further growth

appears to be due to lengthening and thinning of the walls of the alveolar ducts and increases in size of individual alveoli. R. H. D. Short,[22] in an important study of the fetal rabbit and human lung, has shown that artificial distention of the excised rabbit lung at term reproduces the picture of the normal lung at five days after birth. The effect of distention is to subdivide existing spaces by putting the elastic fibers under tension and thus drawing up new septal divisions. Such processes, however, do not explain Broman's observation that the number of generations of branchings increases throughout childhood. In the middle lobe he found 18 generations of branches at birth and 23 to 25 in the adult. In the cow the number in the left middle lobe increased from 33 to 40. The difficult thing to explain is that his count of 18 generations at term included those possessing alveoli, while in the adult 18 generations could be counted before the alveoli were reached. This led Bremer[6] to suggest a peripheral advance of bronchiolar epithelium as a result of which the alveolar ducts of the young are converted into the bronchioles of the adult.

In the mature lung, as in late fetal stages, Loosli and Potter found that the protruding capillaries are covered by blue staining ground substance and connective tissue fibrils. Here and there isolated cells are seen in the interstices of the alveolar walls. Whether these isolated septal cells at this stage represent remaining epithelial cells is difficult to answer. The intimate association of these cells to the underlying connective tissue and their reaction in the inflamed lung suggested to Loosli[17] that they are part of the fibroblast system of the alveolar walls. At least these authors are sure that in the human fetus the cuboidal epithelium does not disappear through any process of swelling, pyknosis, and fragmentation as described in the rabbit lung by Short. Separated by intruding capillaries and then scattered by elongation and distention of the peripheral air spaces, they become so infrequent and isolated that they can no longer be identified as epithelial cells if, indeed, any remain. It is to be hoped that new work with the electron microscope in this laboratory and elsewhere will solve the problem of the nature of the alveolar membrane.

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Note: For references to such major anomalies as the Lobus venae azygos and agenesis of the lung — subjects covered in the lecture but not in this text — see Radiology 58:797-807, 1952; Surgery 31:429-435, 1952.

Lancet Editorial

Medical Education—

Problems of vital interest and concern to all physicians are focused and clarified in the newly published report of the Survey Committee on Medical Education. This report, directed by Dr. John E. Deitrick and jointly sponsored by the Association of American Medical Colleges and by the Council on Medical Education and Hospitals of the American Medical Association, provides us with an amazing amount of factual material collected for a five-year period.

The important problem facing medical education at the time of the Flexner Report on Medical Education in 1910 was that of setting minimum standards of curriculum, faculty personnel, and physical facilities. The problem today is, for the most part, in direct contrast. Curriculum problems now involve maximum limits of material that can be included in a curriculum. The faculty personnel is now in short supply in the basic sciences rather than in the clinical departments. Physical facilities have been vastly improved.

The quality of personnel, rather than quantity of men or money, is the first essential of medical education. This conclusion is voiced both in the Flexner Report of 1910 and the Deitrick Report of 1953. It is essential that faculties recognize and assume their proper function of providing a stimulating educational environment.

The problem of attracting qualified teachers in medicine, particularly in the basic sciences, is in part the low income involved, but also in part a result of the fact that the emphasis on fundamental research in clinical departments is attracting many individuals from the basic sciences into clinical fields. This raises the question as to what place the basic sciences are to hold in the medical curriculum of the future.

Another factor which has discouraged qualified men from making teaching in medicine a career is that selection and advancement of faculty members is frequently based on research interest and ability rather than teaching ability and experience. Faculty members often refer to teaching "load," but seldom to teaching "opportunity."

Adequate education in the use of audio-visual and other refined teaching methods has not been provided for teachers of medicine. Good teachers may be born, not made, but a poor teacher can be made a better one if he has knowledge of a few basic facts about how to put material across to the students. This survey confirms the fact that educational methods vary extremely in the different medical schools in the country. The variety includes all types of educational ideas of the past.

The curriculum is another major source of concern. One problem is what portion of undergraduate medical education is to be occupied by the teaching of habits and technics as opposed to education for understanding. Another is a result of the increasing awareness of the necessity for orienting the physician to the patient as an individual rather than a "case." To do this the student must be provided with thorough knowledge and understanding of all the influences that affect patients, including the social, economic, and emotional environment. The acquisition of a working knowledge in all of these fields, plus mastery of enormously increased medical scientific fact, is an impossible total for a four-year teaching program. What material to forego becomes a crucial decision.

Additional problems include the matter of financing. Present methods of research financing tend to separate the research and educational functions of medical schools to the disadvantage of both. The desirability of maintaining medical education in a university setting must be vigorously reaffirmed. Some solution must be found to the problem of continuing to meet the large and ever-growing budget needs of the medical college, while maintaining other colleges of a university at a comparably high level.

Also, patients for study during the clinical years are becoming increasingly difficult to obtain. Social and economic trends no longer allow a distinction between charity and private patients. Medical schools and teaching hospitals must find some way to utilize private, semiprivate, or insured patients in their teaching program.

Finally, the most important aspect to consider is the effect present educational and training programs are having on the student. The report suggests that the present system does not develop to a desirable degree qualities of independence and leadership.

These many problems are not for the medical educator alone to solve, but deserve the clear, critical thought of all physicians. The quality of medical education will in the last analysis determine the future of medicine in the United States.

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Editor's Note: *We take pleasure in introducing Dr. William F. Maloney as a new member of our editorial staff. Dr. Maloney is assistant dean at the University of Minnesota Medical School.*

The History of American Epidemiology, by C. E. A. Winslow, Wilson G. Smillie, James A. Doull, and John E. Gordon. Edited by Franklin H. Top, 1952. St. Louis: C. V. Mosby Co., 190 pages. $4.50.

At the twentieth anniversary session of the Epidemiology Section of the American Public Health Association in 1949, a special session was devoted to the history of the development of epidemiology in the United States. The four papers presented at this session have been expanded and brought together in this volume.

Each of the authors covers a definite time period. Dr. Winslow's essay deals with the 17th and 18th centuries. Special attention is given not only to the extent to which infectious disease plagued the colonies and the young republic but also to the ideas that were held as to the cause of pestilence. As is usual in his writings, Dr. Winslow presents a sympathetic understanding of the reasoning leading to concepts now known to be erroneous. The second chapter, by Dr. Smillie, deals with the period from 1800 to 1875. The reader is presented with a graphic and factual account of the recurrent waves of yellow fever, cholera, smallpox, typhoid, and diphtheria that devastated the country.

In his chapter on the bacteriologic era, Dr. Doull brings the history of epidemiology up to 1920, portraying the effect of the discoveries of Pasteur, Koch, Smith, and others in giving substance to epidemiology as a scientific discipline that was establishing itself in the United States and having its effect on public health thinking and practice. In the final essay entitled "The Twentieth Century — Yesterday, Today and Tomorrow," Dr. Gordon portrays current concepts of the epidemiology of infectious diseases and attempts to show the possible extension of epidemiologic methods and principles to the study of noninfectious conditions in the epidemiology of tomorrow.

This is a book of more than limited interest. The epidemiologist will find it a valuable summary of American developments and progress. The clinician and general scientist will find here a gold mine of information regarding the history of infectious disease in this country. The lay reader will find it an invaluable account of an important and little known aspect of American history.

Gaylord W. Anderson, M.D.

Office Psychiatry, by Louis C. Moench. *Chicago*: Year Book Publishers, Inc., 300 pages. $6.00.

This book is an attempt to show in a concise simple manner how emotional problems can contribute to the cause of many medical illnesses and can complicate and influence the course of still others. The author strives to present the many psychiatric concepts in simple, clear, and useful terminology that can be understood and applied by students and practitioners even in the absence of any special training in this specialty. This small volume is well presented and very cleverly illustrated. In his chapter on "the interview" the author presents a series of very useful and practical suggestions that will prove most beneficial in the development of better patient-physician relationship. Considering the magnitude of the problem, this book is well done and should prove most useful to the general practitioner.

A. B. Baker, M.D.

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The Biochemistry of Gastric Acid Secretion, by Edward J. Conway, M.D., D.Sc., F.R.C., F.R.C.P.I., professor of biochemistry and pharmacology, University College, Dublin, Ireland, 1953. Springfield, Illinois: Charles C Thomas, 185 pages. $5.00.

The author brings together evidence for the various theories of acid secretion in a compact and logically presented form. Beginning with a brief description of the anatomic, histologic, and physiologic background, which has been firmly established, the ideas which have been evolved to account for the source of the hydrogen ions, the energy factors associated with their transfer across membranes, and the chemical mechanisms involved in both, are reviewed clearly and with adequate documentation of the original literature. Comparisons to acid formation by yeast cells are included. Finally, a discussion of the significance of gastric urease is presented.

The viewpoint and judgments favored by the author will not be accepted by all workers in the field, and the interpretations given should be thought of as tentative.

Of particular interest to the clinician may be the discussion of the role of gastric urease. The ammonia liberated by this enzyme neutralizes a certain amount of acid, and the conclusion is drawn that "Evidence amounting to proof is given that the gastric urease in the human subject has a functional significance in neutralizing gastric acidity and protecting the mucosa." This reviewer would prefer to see the evidence corroborated in other laboratories before accepting the statement, as given, because it depends solely on the data of FitzGerald and associates at University College and St. Vincent's Hospital, Dublin.

Certain conclusions of this group are in conflict with those of others, that is, they claim to have demonstrated the presence of gastric urease in all species studied including the pig, while repeated tests for the enzyme in this species proved negative in the laboratories of Linderstrøm-Lang and others including the present reviewer's. That urease might function intramucosally in a protective way by furnishing ammonia to neutralize acid is a plausible, but not a proved, theory. That the enzyme acts to control the acidity of the gastric juice is still open to considerable question, as indicated by work which appeared after this book was written. Uremic conditions with their high blood urea levels would be expected to result in lowered gastric acidities according to the postulated role for urease, but the clinicians who have been consulted by this reviewer are unaware of any such direct association. It may exist but it does not seem to have been demonstrated. In view of the beneficial effects claimed by FitzGerald from urea administered per os in gastric ulcer patients, it should be worth while to test this therapeutic approach in other clinics, but until this is done it might be better to hold to a somewhat more conservative position than that taken by the author in his rather complete acceptance of FitzGerald's conclusions. This does not detract from the basic value of the book which is the summation in a single well presented source of widely scattered data on controversial subjects of the mechanism of gastric acid secretion.

David Glick, M.D.

(Continued on page 524)

The Journal Lancet

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

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AUTHOR INDEX

American College Health Association News . . .

A number of people are responsible for the news items this month. We wish to thank each one of them and to encourage more of you to send us information about *your* Health Service.

W. McKenna, director of the Xavier health service, reports that Doctors Albert Bloom and George Thomas have been added to their medical staff. He also reports the following activities: The entire student body received a chest x-ray and blood test in October as a part of the entrance examination; the Third Annual Food Handlers Conference directed by the New Orleans Health Department was held for college personnel on October 23, 27, and November 4; dormitory inspections were scheduled in November as a part of the Environmental Health Program; the director of the health service and Miss Cleo Moran of the physical education department attended the Louisiana committee meeting on Health Education for Teachers at Southern University November 5, 1953.

* * * *

Wayne University Health Service also has new staff members. Dr. Henry Holt, who replaces Dr. Barbara Hardt, has been assigned to medical supervision of the athletic program of the University, and Dr. Mary Dickson has begun her duties as staff psychiatrist. She replaces Dr. Donald Carson, who has returned to Canada to enter private practice. Mr. Lyle Ward, formerly with the Family Service Society of Detroit, has accepted a position with the mental hygiene staff.

* * * *

Sanford E. Ayers, M.D., director of the student health department at the University of Florida, has been sending us their monthly reports, from which we have gleaned the following information. During August the staff was augmented by the arrival of Dr. Dorothy E. Shelly, who came from the student health service of the University of Illinois. The September report tells of the first week of registration, which was a very busy period with the clearing of all new students through the infirmary in addition to the regular patient load. A total of 2,995 freshmen and transfers were given health clearance during the month. Those with no defects which would restrict physical activity, as noted on preentrance physical examination reports, were automatically cleared for regular physical education classes and, in the case of men, for R.O.T.C.. About 15 per cent of the total, with reported defects, were reexamined and about 10 per cent were classified for restricted activities. The patient load for September was considerably in excess of the load for the corresponding months of 1951 and 1952. Part of the increase was due to an unusually high incidence of upper respiratory infections. The following is an interesting comparison in attendance:

September	*1951*	*1952*	*1953*
Total hospital days	98	139	185
Outpatient treatments	4722	4791	7326

Four new nurses were welcomed to the staff: Mrs. Sydell Leonard, Mrs. Donna Gannon, Mrs. Roberta Winters, and Miss Margaret Cook (part-time).

* * * *

The Twenty-ninth Annual Meeting of the Ohio College Health Association was held on October 23 and 24 at Ohio University. The following is a brief outline of the program:

A tour of the health center was made on Friday morning. The general theme of the Friday afternoon session was "How to find and help the divergent student," with E. H. Hudson, M.D., Ohio University, presiding.

Subjects discussed were: "Speech correction; why?"—A. C. LaFollette, Ph.D., associate professor, dramatic art and speech, Ohio University; "Physical rehabilitation"—Arthur S. Daniels, Ph.D., professor of physical education, Ohio State University; "Dysmenorrhea not an entity"—Eleonora L. Schmidt, M.D., Ohio University; "Decreasing the divergent angle"—W. S. Hawn, Marietta College, presiding.

Max L. Durfee, M.D., Oberlin College, presided at the annual dinner. The dinner speaker was J. Arthur Myers, M.D., professor of medicine, preventive medicine, and public health, at the University of Minnesota. His topic was "Tuberculosis among College Students; yesterday, today and tomorrow."

William T. Palchanis, M.D., Ohio State University, presided at the Saturday morning session, when Dr. Myers addressed the group on "When Does Tuberculosis Begin?" R. H. Browning, M.D., led the discussion which followed.

Mrs. Mildred Crane, R.N., Otterbein College, presided at the meeting of the Nurses' Section.

* * * *

The fourth National Conference on Physicians and Schools was held at Highland Park, Illinois, September 30 through October 2. The conference was divided into subject groups which discussed particular problems informally and made reports at a general session on the final day.

One discussion group presided over by Dr. Leland M. Corliss, director of health services in the Denver public schools, pointed out the importance of adequate screening of candidates for teaching positions; the need for a freer exchange of health information by schools, families, and private doctors so as to assist the teacher in the proper management of her pupils; and the valuable contribution that nurses serving in high schools can make as health counselors.

For the first time a discussion group considered mental health aspects of teaching in the classroom. Walter E. Hager, president of Wilson Teachers College, Washington, presided over the group. It was agreed that teachers strongly affect the mental and emotional health of children and that, for this reason, teachers must be thoroughly well-adjusted persons in order to carry out proper teaching approaches. The group felt that there is a need to establish criteria that would raise the standards for selection of teachers and suggested that an organization, such as the National Education Association, undertake setting up a committee whose aim would be to establish such criteria.

The importance of health appraisal data on children was the subject of another discussion group, with Miss Gertrude E. Cromwell, supervisor of nursing in the Denver public schools, as the chairman. It was suggested that practicing physicians, school health workers and teaching personnel, parents, and community health agencies should be involved in such an interchange. While

the confidential nature of some of the information must be respected, the value of such data as a child's physical ability, his handicaps, his mental or emotional status, and his home conditions in effecting a proper adjustment in school was emphasized.

Many other subjects, ranging from family responsibility for a child's health to desirable health standards for sports programs in both elementary and high schools, were considered.

° ° ° °

An announcement from the National Jewish Hospital in Denver was received from Philip Houtz, executive director. This hospital is equipped to render treatment at no cost to students who are in need of hospitalization because of tuberculosis or chest diseases and who are unable to pay for care. The hospital's facilities are available without regard to race or creed. The hospital imposes no time limit; and patients may stay for as long as they can benefit from the hospital's facilities. For further information, write to Mr. Houtz.

° ° ° °

As a result of our annual check on the directors of student health services of member institutions, we find that the following changes have been made:

Institution *New Director*

University of Alabama — Walter C. Folsom, M.D.
Allegheny College — Samuel E. Hoke, M.D.
Boston University — Samuel E. Leard, M.D.
Bowling Green State University — Mrs. Jane D. Igou, (administrator)
University of Buffalo — Wanda Galantowicz, M.N.
Columbia University, College of Physicians and Surgeons — Albert R. Lamb, Jr., M.D.
Cornell College — Joan Taylor, R.N.
Cottey College — Marjorie Deily, R.N.
Denison University — Lawrence H. Miller, M.D.
University of Denver — Lewis Barbato, M.D. (acting director)
Earlham College — Helen Finley, M.D.
Eastern Illinois State College — Lauro R. Montemayor, M.D.
Fort Hays Kansas State College — G. C. Hutchison, M.D.
George Washington University — Howard Robert Unger, M.D.
Haverford College — William Lander, M.D.
University of Illinois — L. M. Dyke, M.D.
University of Kentucky — J. S. Chamberg, M.D.
Michigan State College — Clifford G. Menzies, M.D.
Midland College — Mrs. Margaret Morris, R.N.
University of Missouri — George X. Trimble, M.D.
Montana State College — R. B. Farnsworth, M.D.
National College of Education — Mary H. Pope, M.D.
New York State Teachers College at Cortland — Lawrence Z. Shultzaberger, M.D.
North Carolina College — Charles Watts, M.D.
Queen's University — H. M. Campbell, M.D.
Skidmore College — Claire K. Amyot, M.D.
Stout Institute — Miss Shirley Kuhn, R.N.
Syracuse University — G. Arnold Cronk, M.D., (acting director)
Union College — Alexander Arony, M.D.
Union Theological Seminary — Howard W. Brown, M.D.
College of William and Mary — Ben T. Painter, M.D.

News Briefs . . .

North Dakota

The state health planning committee has given final approval for a $1,082,000 construction program at the Jamestown State Hospital. The project will be financed by $800,000 in funds appropriated by the 1953 legislature and $282,000 in federal money allowed North Dakota for hospital construction. Dr. R. O. Saxvik recommended that the money be used for a new admitting hospital and a ward building. Construction is expected to start next spring.

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A new clinic was opened in Garrison this fall. The ranch-type structure contains 22 rooms in addition to the pharmacy, reception area, waiting room, and library. The staff is headed by Drs. John Boyle, Charles Schnee, and Martin Hochhauser.

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Riverdale's 12-bed hospital became a clinic November 1. Due to lack of patients, further operation of a hospital was said to be impractical.

° ° °

Dr. L. W. Larson, Bismarck, was recently honored by the presentation of a scroll of merit from the American Society of Clinical Pathologists at the annual convention in Chicago. Dr. Larson also a short time ago received a certificate award for fifteen years of service in the prevention of cancer at a meeting of the Burleigh County Cancer Society.

° ° °

Dr. Charles A. Arneson, Bismarck, has been elected an associate in the International College of Surgeons. The honor was bestowed upon Dr. Arneson at the annual convention held in New York City.

° ° °

Dr. Syver Vinje, a physician at Hillsboro for forty years and a member of the medical profession for more than fifty years, retired November 1. Dr. Vinje has been city health officer since 1915, served in the state senate from 1934 to 1938, served nine years on the board of education, and was chairman of the Traill County Red Cross chapter from 1924 to 1928. Last year Dr. Vinje was honored by the state association, awarded a certificate, and made a member of the unit's 50-Year Club.

° ° °

Dr. O. M. Smith, who practiced in Killdeer and the surrounding territory before his retirement several years ago, was honored November 29. The Killdeer Town Criers sponsored "Doc Smith Day" and were assisted by local organizations and a county-wide committee selected to help coordinate the day's activities. A reception and open house were held in the school gymnasium. Dr. Smith was one of the last of the old-time country doctors in North Dakota to retire.

° ° °

Dr. Cecil C. Smith, Mandan, has been appointed chief of medical services in the state health department. Dr. Smith will retain his position of health officer of the Custer public health district, although he will maintain offices in the health department at the Capitol.

° ° °

Dr. Lad J. Kucera has been appointed chief medical officer of the Fargo Veterans Hospital, succeeding Dr.

Roy R. Quamme, who is being transferred to the Veterans Administration office in Detroit.

* * *

Dr. P. F. Christenson, a graduate of the University of Chicago School of Medicine in 1942, has joined the DePuy-Sorkness Clinic in Jamestown as a specialist in radiology. Dr. Christenson has practiced in Nebraska, Utah, and recently in Oregon.

* * *

Dr. Clyde L. Smith has joined the staff of the Missouri Valley Clinic at Bismarck. A graduate of the University of Minnesota Medical School, Dr. Smith has been practicing in St. Paul for the past four years.

* * *

Dr. William M. Buckingham joined the staff of the Elgin Hospital in Dickinson November 1. Dr. Buckingham received his medical degree from Bowman-Gray University and for the past year has practiced medicine in Hillsboro.

* * *

Dr. J. F. Connor, of Winnipeg, has joined Dr. J. F. Johanson in the practice of medicine and surgery in Cavalier.

* * *

Dr. V. A. Mulligan, who has practiced in Langdon for the past 22 years, has opened a new practice in Phoenix, Arizona.

* * *

Dr. Robert E. Hankins, a graduate of the Loyola University Medical School, has opened a practice in Mott.

* * *

Two North Dakota physicians have recently been discharged from army service and returned to their former practices in the state. They are: Dr. Robert D. Schoregge, who has rejoined the surgical staff of the Quain and Ramstad Clinic in Bismarck, and Dr. Edwin O. Hieb, who has resumed his association with the DePuy-Sorkness Clinic in Jamestown.

Minnesota

Members of the 1932-33 medical school class of the University of Minnesota held a special reunion at Homecoming. They presented more than $2,500 to the medical school for scholarships. Dr. H. S. Diehl will head the committee responsible for selecting recipients for the scholarships. Dr. E. T. Bell, emeritus professor of pathology, spoke at a dinner meeting of the alumni in St. Paul. His subject was "The University of Minnesota Medical School from 1928 to 1932." At a series of Homecoming clinics, two of the speakers were Dr. Reuben Berman and Dr. Robert Kierland, both 1932-33 alumni.

* * *

Fifteen cancer research projects will be carried on at the University of Minnesota during the next year under terms of a $75,000 grant from the American Cancer Society.

Subjects of the studies and researchers who will conduct them are: role of the pituitary gland in breast and adrenal tumors in mice, Dr. Carlos Martinez; study of the chemistry of cancer and the role of sulfhydryl compounds, Dr. Isaac M. Kolthoff, and Dr. Maurice B. Visscher; radium treatment of cancer of the uterus, Dr. Roy G. Holly and Dr. John L. McKelvey; statistical studies in the tumor clinic and followup of patients, Dr. Zimmerman and Dr. Claude R. Hitchcock; studies of human cancer with newly developed methods, Drs. James R. Dawson, Joel G. Brunson, Robert Hebbel, and Gunnebejor Aurebeck.

Others are: studies of hormones in human and animal cancer, Drs. John J. Bittner, W. D. Armstrong, and Saul L. Cohen; irradiation of lymphoid tumors, Dr. Charles M. Nice, Jr.; study of normal and cancer stomachs by new physical methods, Dr. David Glick, methods for earlier diagnosis of lung cancer, Drs. Leo G. Rigler and Richard L. Varco; study of x-ray effects on tumor-bearing tissues, Drs. K. W. Stenstrom, James F. Marvin, Robert A. Ledner and Donn G. Mosser; search for an intravenous dye as a cancer detection agent and technical problems in gastric and esophageal cancer surgery, Drs. Owen H. Wangensteen, William D. Kelly, and Edwin L. Brackney; study of dietary production of anemia and precancerous conditions in swine, Drs. Jay Sautter, Hitchcock, and J. Bradley Aust; clinical, endocrine and metabolic studies relating to cancer surgery and surgical removal of adrenal glands, Drs. Zimmermann, Hitchcock and Henry S. Block; study of effects of exhaust fumes on incidence of lung cancer in mice, Dr. Hitchcock; and treatment of breast cancer with hormones and radiation, Dr. Byrl J. Kennedy.

* * *

The University of Minnesota has been awarded a two-year $25,503 contract by Randolph Field Aviation Medical School to conduct research on effects of exposure to high concentrations of carbon dioxide. Dr. Ernest B. Brown, associate professor of physiology, is in charge of the project.

* * *

Plans to organize a Minneapolis chapter of the National Multiple Sclerosis Society were discussed at a recent meeting. Dr. A. B. Baker, head of the neurological department at the University of Minnesota, spoke on the characteristics and scope of the disease.

* * *

The Minneapolis War Memorial Blood Bank celebrated its fifth anniversary on Armistice Day. The Minneapolis Junior Chamber of Commerce was largely responsible for starting the institution. It canvassed other groups and raised $50,000. Minneapolis hospitals advanced $15,000 for equipment and the Hennepin County Red Cross $20,000 for starting capital. The Red Cross also donated $5,000 worth of World War II blood center equipment. Dr. G. Albin Matson, director of the bank, states that "transfusions are safer, reactions fewer, and that blood bank services are more complete than they ever could have been in individual hospital blood banks."

* * *

More than 40,000 mice have been moved into Elias P. Lyon hall, the new University of Minnesota medical research laboratory. The mice will be used by Dr. J. J. Bittner in cancer research. The new building is not completed as yet, but dedication is tentatively set for February 11.

* * *

Dr. Frank Hammond Krusen, a member of the staff of the Mayo Clinic and professor of physical medicine and rehabilitation at the University of Minnesota Mayo Foundation, has been selected to receive the second annual physician's award of the president's committee on employment of the physically handicapped. The award will be presented at the annual meeting of the Congress on Industrial Health in Louisville, Kentucky. Dr. Krusen was chairman of the Baruch committee on war and postwar rehabilitation in 1944 and is past president of the American Congress of Physical Medicine.

Dr. Owen H. Wangensteen, chief of the department of surgery at the University of Minnesota, has been appointed to serve on the National Advisory Heart Council. The appointment was announced by Leonard A. Scheele, surgeon general of the U. S. Public Health Service.

o o o

Dr. David Anderson of Austin has been elected president of the Minnesota division of the American Cancer Society.

o o o

Dr. John Freeman is resigning as assistant superintendent of the Fergus Falls state hospital to become clinical director of the North Dakota state hospital at Jamestown. His resignation will become effective February 1.

South Dakota

Faculty members of the medical school at the University of South Dakota have received more than $105,000 for research in medicine from federal and philanthropic agencies. The faculty carries on the research in the summer and during their spare time. In order to secure a grant, the investigator must prepare a proposal outlining the aim of the study, plan of operation, and the significance. The proposal is then referred to a group of experts in the field. If the subject is not being investigated elsewhere and is of potential value to science, approval is given and the award made.

o o o

A session of postgraduate study was held by the American Academy of General Practice at the Marvin-Hughitt Hotel in Sioux Falls September 19 and 20. An intensive course of nine lectures on endometriosis was given by three doctors from the Department of Obstetrics and Gynecology at the University of Minnesota Medical School. Dr. A. P. Reding, Marion, is president of the Academy, Dr. Robert A. Buchanan, Huron, president-elect, and Dr. John A. Kittelson, Sioux Falls, secretary.

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A new medical clinic was opened at Carthage on September 5. Dr. Karlis Avots is director of the clinic.

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Plans are being formulated for a $350,000 fund campaign for a new 50-bed wing for McKennan Hospital in Sioux Falls. Plans involve a $900,000 program including construction of the 50-bed wing, remodeling, and additional equipment and furnishings.

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Dr. H. L. Saylor, of the Huron Clinic, was honored at a dinner on August 27, commemorating his retirement on September 1 after 39 years of practice.

o o o

Dr. Regin Reagan, Sioux Falls, was elected the state's general practitioner of the year by the South Dakota Medical Association. Dr. Reagan will represent South Dakota in national competition sponsored by A.M.A.

o o o

Dr. C. H. Dulaney, who practiced in Canton for twenty-two years, was appointed a member of the Veterans Hospital staff at Ft. Meade. Dr. Dulaney joined the staff November 1, and is serving as senior consultant and specializing in neuropsychiatry.

o o o

Dr. E. T. Gough, administrator of the Methodist State Hospital at Mitchell, has been chosen president of the South Dakota Hospital Association.

o o o

Dr. Nathaniel Whitney, a specialist in children's diseases, has joined the Dawley-Kegaries Clinic in Rapid City. Dr. Whitney received his premedical training at Harvard University, his medical degree from the University of Cincinnati College of Medicine, and for the past two years has been with the Air Force at Robins Air Force Base, Georgia.

o o o

Dr. Warren S. Peiper has succeeded Dr. John T. Murphy as radiologist and x-ray diagnosis and therapy specialist at the two Mitchell hospitals. Dr. Murphy resigned to accept a similar position at Sturgeon Bay, Wisconsin.

Deaths . . .

Dr. M. W. Roan, who practiced medicine in Bismarck from 1906 until his retirement in 1947, died in a Bismarck hospital September 6. He was one of the founders of the Missouri Valley Clinic.

o o o

Dr. Fred W. Fergusson, who practiced for some years in Kulm, North Dakota, died at Lodi, California, on September 5. Dr. Lodi received his premedical training at North Dakota University and took his medical degree from Northwestern University.

o o o

Dr. Jacob H. Miller, 72, former operator of a sanitarium in Bismarck, North Dakota, died November 13. Dr. Miller moved to California after his retirement in 1941.

o o o

Dr. Myron O. Henry, Minneapolis, died August 31. Dr. Henry, a member of many medical groups, was an orthopedic surgeon and served on the faculty of the University of Minnesota Medical School.

o o o

Dr. Arthur Edwin Benjamin, 84, a Minneapolis surgeon for more than 60 years, died October 1. Dr. Benjamin received his medical degree from the University of Minnesota in 1892. He served the University medical school until 1938 when he was given rank of professor emeritus.

o o o

Dr. George H. Schlesselman, 68, Bloomington, Minnesota, died November 3. Dr. Schlesselman was on the staff of Anoka State Hospital for the past two years. Prior to that he was on the staff of Swedish Hospital in Minneapolis for twenty-five years.

o o o

Dr. O. F. Mellby, 77, physician and surgeon at Thief River Falls, Minnesota since 1907, died November 5. A memorial fund for Dr. Mellby may be used to provide a new altar for Trinity Lutheran Church. Dr. Mellby was chairman of the board of deacons of Trinity Church.

o o o

Dr. Edward Elsey, 50, a physician at Glenwood, Minnesota, died November 15 after suffering an accidental bullet wound while on a hunting trip.

o o o

Dr. Fred L. Bregel, 64, St. Paul, Minnesota, died November 13. Dr. Bregel practiced medicine in St. James for twenty-nine years before joining the veterans administration rating board staff at Fort Snelling eleven months ago. Dr. Bregel was a past vice president of the Southern Minnesota Medical Association and a member of the Tri-County Medical Society.

o o o

Dr. Raymond P. Frink, 76, a South Dakota physician for more than fifty years, died October 25. Dr. Frink has been physician at the Redfield State Hospital for the past eight years.

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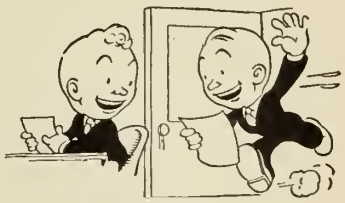

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BOOK REVIEWS

(Continued from page 514)

Body Temperature: Its Changes with Environment, Disease and Therapy, by W. A. Selle, 1952. Springfield, Illinois: Charles C Thomas, 112 pages. $3.50.

This American lecture series monograph is a competent review which covers in summary fashion the main aspects, both physiologic and clinical, of body temperature. Though it is not the plan of such a small book to penetrate deeply into any particular portion of the field, it does provide a worth-while introduction of the subject for the beginning student or an easily comprehended synopsis for one with only casual interest. The bibliography is brief but it contains the important publications that can lead a student on to the vast literature of the subject. The organization is good, the writing is lucid, and many of the figures are helpful, but the tables—subtitled as figures in the book—are unnecessarily confusing.

F. John Lewis, M.D.

The Principles of Neurological Surgery, by Loyal Davis, M.D., Ph.D., D.Sc., (Hon.), professor of surgery and chairman of the division of surgery, Northwestern University Medical School, 1953. 544 pages, 186 engravings, 354 illustrations. Philadelphia: Lea & Febiger. $8.50.

This is the fourth edition of Dr. Davis' book. Like its predecessors it deals with the general principles of neurologic surgery as applied to general diagnosis, therapy, and prognosis. Additions have been made to include material on the use of radioactive isotopes, angiography, and some of the recent developments in treatment. Otherwise, there is little change from the preceding edition. Most of the previously present inconsistencies and contradictions have again been included. Probably the magnitude of the production prevented revision of this somewhat confusing editorial style. The book is written primarily as a textbook for medical students and this style detracts from its usefulness.

The book is comprehensive. It deals with all the important neurosurgical lesions. Dr. Davis has made a determined effort to present the material from a clinical viewpoint. He has included all necessary neuroanatomic and neurophysiologic data required to understand properly the clinical development of the lesion and the scheme of therapy. He begins with a thoroughly instructive chapter on the technic and significance of the neurologic examination. Thereafter, the various lesions of the nervous system are discussed. These include injuries, tumors, and infections of the skull, brain, spinal cord, and peripheral nerves. The remainder of the book includes material on the treatment of intractable pain, sympathetic nerve surgery, surgery of the convulsive disorders, vascular malformations, anomalies of the neural axis, psychoses, and abnormal involuntary movements. These last chapters, in particular, round out this edition and enhance its value.

This book is not intended as a reference work. An adequate bibliography is presented, but the opinions expressed are primarily those of Dr. Davis. There are 354 illustrations; all seem to be well selected to demonstrate the desired data.

Lyle A. French, M.D.