

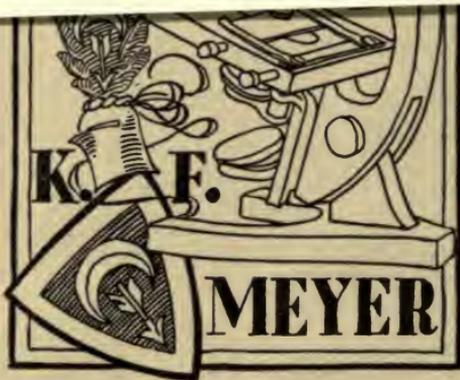




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**PROTEIN THERAPY**  
**AND**  
**NONSPECIFIC RESISTANCE**



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PROTEIN THERAPY  
AND  
NONSPECIFIC RESISTANCE

BY

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“Thus there exists a fashion in medicine, as in the other affairs of life, regulated by the caprice and supported by the authority of a few leading practitioners, which has been frequently the occasion of dismissing from practice valuable medicines, and substituting others less certain in their effects and more questionable in their nature. As years and fashions revolve, so have these neglected remedies, each in its turn, rise again into favour and notice, whilst old receipts, like old almanacks, are abandoned until the period may arrive, that will once more adapt them to the spirit and fashion of the times. Thus it happens that most of our “*New Discoveries*” in the *Materia Medica* have turned out to be no more than the revival and adaptation of ancient practices.”

—From the Introduction of Paris’  
*Pharmacologia*, New-York, 1830.



## PREFACE

The conception that the organism in its resistance to disease and defense against bacterial invasion depends on biologic reactions essentially specific has dominated medical thought, medical experimentation, and medical practice for a period of over thirty years. They have been years of tremendous progress in the theory and the practice of medicine. Indeed, the advance, as contrasted with that of the ages gone before, has been so vast and far-reaching that we have by association come to regard this progress and the underlying trend of medical thought and theory, i.e., specificity, as practically identical.

The idea of therapy on a nonspecific basis seems therefore at first glance a step backward, investigation of such a subject illogical, if nothing worse. And as we might expect on such premises, the present interest in nonspecific therapy did not originate on the basis of a convincing theory or promising laboratory experimentation. It was the clinic that forced upon our attention certain therapeutic results which could not be ignored, results so startling in many ways that our conception of the mechanism of recovery from disease has had to be recast.

The theoretic basis to account for the results has been lacking, at least our current conception of immunity and of resistance to disease has been found wholly inadequate to explain the clinical results. This seeming empiricism, this lack of exact knowledge concerning the mechanism of the nonspecific reaction has been the chief point of attack for whatever criticism has been presented. A brief examination of the subject will, however, reveal that nonspecificity need not be as illogical, theoretically, as a cursory view might lead us to believe. If we keep the focus of our attention on the reaction of the body to injury—on inflammation—we find that this reaction, no matter how produced,—be it bacterial invasion, intoxication, or trauma,—is fundamentally similar under all circumstances. The type of cellular reaction may vary to some degree, the amount and composition of the exudate may differ, but the basic alterations are always alike. We deal with a consistent effort to dilute the noxious agent, to remove it by intracellular or extracellular digestion, to neutralize it; these failing, then to wall it off, to put it outside of the current of normal tissue activity.

If now we seek to alter this process therapeutically we have two distinct avenues of approach. The one is interested solely in the cause of the inflammatory reaction—if a bacterium, to produce an anti-

bacterial agent—if a toxin, to produce an antitoxin—if a chemical, to introduce a neutralizing substance. We see at once that in so far as the causes of inflammation may be unlimited, so our specific agents would have to be unlimited.

The alternative lies in the endeavor to alter the inflammatory reaction of the body itself. We may seek to augment its natural course, hastening autolysis and resorption, or attempt the reverse, retarding autolysis and stimulating the reparative phases, as we may wish. This is a true "ergotropic," as v. Groer has termed it, a therapeusis whereby we alter the reaction of the organism to the etiologic agent, rather than endeavoring to influence the causative factor of the inflammatory process directly. Such a therapy must of necessity be nonspecific in the immunological sense.

Perhaps it will be well to make clear at the very beginning that the nonspecific reaction brings into play no new and heretofore unknown factors of resistance. It deals largely with reactions previously studied and which have always been employed by the organism in overcoming disease, with or without our conscious interference. It does deal, however, with the stimulation of these forces and when skillfully invoked brings to bear a summation of the varied measures of defense of which the organism is possessed. It is quite probable that these potential forces may have been latent or held in abeyance until the nonspecific reaction brings them into activity. It has been observed that the antibodies (agglutinins, precipitins, opsonins, etc.) are "shed" or cast off from the cells after a nonspecific injection; so, too, fibrinogen and thrombokinase are increased and a variety of enzymes are poured out from the cells into the circulation.

If nonspecific therapy is after all merely a method that deals with heretofore known reactions we must be prepared to accept the probability that it obeys all the commonly observed laws of biologic reactions. If we regard it as a method of stimulation—plasma activation—it follows that it can only be effective when the protoplasm is still in fit condition to respond to stimulation. Once the stage of exhaustion has been reached the mere irritation of the nonspecific agent is no longer able to bring about any alteration in the disease process other than an aggravation.

The observations that have been made the basis of this monograph have been gathered partly at first hand, both clinically and experimentally, more largely from a survey of such literature as the exigencies of the war have made available to me. The summarizing of our present knowledge in this particular field has seemed of some possible value, not with the idea of popularizing a new therapeutic measure but rather in stimulating interest in a direction that seems to offer decided possibilities of advance. I have therefore merely indicated some of the methods at present employed in nonspecific therapy without effort to define precise modes of application or indications for

therapeutic use. On the other hand I have endeavored to present the possible theoretical basis and some of the collateral fields of application as fully as our present knowledge will permit. A great number of problems and questions of decided practical importance could unfortunately be merely mentioned without further discussion.

In the presentation of the clinical results so far reported I have endeavored to maintain an attitude of caution. If at times I have erred from pure objectivity I must accept the blame in perhaps presenting the clinical reports of a number of observers whose enthusiasm has perchance outweighed their judgment. We must remember that it was the clinic that directed the attention to this form of therapy.

During the short space of seven years nonspecific therapy has gained a firm foothold in clinical thought and practice; to-day it is recognized even by immunologists as one of the factors in resistance to disease. Whether, as Much surmises, nonspecific resistance and nonspecific immunity are of greater importance to the organism than are the specific forces should not for the time being concern us; our interest should be centered on applicability, methods and causes. Only when the vast field has been partially explored will it be permissible to judge the ultimate importance.

While I have retained the name Protein Therapy, it should be recognized that Protein Therapy deals merely with one of a large group of agents which can be used to elicit the nonspecific reaction. Other terms have been applied—"Colloid Therapy"; "Shock Therapy"; "Foreign Protein Therapy"; "Heterovaccine Therapy," but inasmuch as it is the reaction of the patient that is of importance, not the substance that causes the reaction, a name much broader in its significance should be used. "Ergotropie," the term coined by v. Groer, is possibly correct and most expressive in that it emphasizes the reaction of the patient and properly ignores the substance that causes the reaction.

How far-reaching the field of nonspecific stimulation is in its various modifications becomes apparent from a consideration of the number and the character of the agents which have been employed to bring about therapeutic results. Even the purely physical and mechanical means—including irradiation, electricity, baths, massage, etc.—must be included in the survey because in some measure they bring about changes in the organism similar in character to those that we shall discuss in the following pages.

To Dr. Otto L. Schmidt, who very kindly read the manuscript and made a number of suggestions, and to Dr. Joseph L. Miller, whose interested coöperation I have at all times enjoyed, I am under grateful obligation. To Miss Josephine Bates of New York I am indebted for her careful revision of the bibliography.

W. F. P.



## INTRODUCTION

Seven years have elapsed since the attention of the profession was first seriously attracted to the nonspecific character of vaccine therapy. The literature previous to this, however, contained considerable evidence suggesting this viewpoint. Immunologists and members of the medical profession were so engrossed with the idea that favorable results could only be secured by specific means that this evidence was largely ignored.

As a consequence of the stimulation given by the earlier investigators there has developed an extensive literature upon this subject. A considerable number of agents, many of them proprietary in character, have been recommended as possessing special virtues. The marked febrile reaction with its accompanying shock inherent in the more toxic substances first used in this form of therapy prevented its widespread adoption. This may be considered as most fortunate. It is well that this procedure was restricted until more unanimity of opinion was established in regard to indications, dosage and therapeutic value. Indiscriminate use of any new and more or less untried method of treatment, especially when associated with possible danger, is to be discouraged. Its application in conditions where it is not indicated would tend to place it in bad repute and might delay the development of a method of real but possibly limited value.

It is opportune, therefore, that this subject be fully presented to the profession by some one familiar with the problems of immunity, well informed upon the literature of Protein Therapy, and who at the same time has enjoyed clinical experience in its application. Dr. Petersen, in conjunction with Dr. Jobling, were the American pioneers in this work. Through their carefully controlled clinical observations and logical deductions they have stimulated other investigators.

To all those interested in the treatment of infections—and this includes both physicians and immunologists—this book will be most welcome, presenting as it does in a comprehensive manner a complete analytical review of the subject, which will be of assistance in furnishing a basis for further carefully controlled studies.

JOSEPH L. MILLER.



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PROTEIN THERAPY  
AND  
NONSPECIFIC RESISTANCE



# PROTEIN THERAPY

## CHAPTER I

### THE HISTORY OF PROTEIN THERAPY

The remarkable fact that some individuals are resistant to infectious disease while others are not; that of two seemingly equally strong individuals, the one may die, the other recover from the same infection, has always interested biologists and physicians.

Naturally enough the efforts to explain resistance to disease have varied with the mode of biological thought current at any given period. It was not until the development of our instruments of precision made possible the work of Pasteur and of Koch that the study of the causal relation of micro-organisms to certain disease processes diverted the interest of the medical mind from the philosophic tendency that had characterized the early half of the last century, to the concrete, the direct, the specific ideation upon which modern science is founded. Naturalistic generalization gave place to accurate biological observation. And with pathological and bacteriological definition of disease processes, the mental attitude of the physician likewise changed in regard to resistance to disease as a general phenomenon to inquiry regarding resistance to specific disease processes.

The brilliant era of specificity in therapeutics that was ushered in by the work of v. Behring, the fascinating serological researches of Ehrlich and of Bordet, the discovery of the specific spirochætecide by Ehrlich in the field of chemotherapy, stamped with the seal of success these years of medical advance—advance made wholly on a background of the strictest specificity. Naturally enough in such a period of successful achievement, minor currents passed unnoticed. Clinical observations that did not fit in with the prevailing mode of thought were but half heartedly put forward and soon passed into oblivion. Wright but recently pointed out a few such instances that came to his attention during the past twenty years:

. . . "I confess to having shared the conviction that immunization is always strictly specific. Twenty years ago, when it was alleged before the Indian Plague Commission, that antiplague inoculation had cured eczema, gonorrhœa, and other miscellaneous infections, I thought the matter unde-

servicing of examination. I took the same view when it was reported in connection with antityphoid inoculation that it rendered the patients much less susceptible to malaria. Again, seven years ago, when applying anti-pneumococcus inoculation as a preventive against pneumonia in the Transvaal mines, I nourished exactly the same prejudices. But here the statistical results which were obtained in the Premier Mine demonstrated that the pneumococcus inoculation had, in addition to bringing down the mortality from pneumonia by 85 per cent., reduced also the mortality from other diseases by 50 per cent. From that on we had to take up into our categories the fact that inoculation produces in addition to 'direct' also 'collateral' immunization." . . .

Several other observations must be recalled. In 1893 Eugene Fränkel reported on the treatment of some 57 cases of typhoid fever treated with subcutaneous injections of typhoid bacilli. The results were promising. In an address delivered at the same time Rumpf presented a similar series of typhoid patients, but treated with subcutaneous injections of a pyocyaneus vaccine. Rumpf based his work on the experiments of Buchner and his pupils who had emphasized that in tuberculosis, the infection then under most intensive study in Germany, not only tuberculin but other bacterial products could activate previously latent powers of resistance. Römer, working along the same line, had found that tuberculous animals could be killed by extracts obtained from pneumobacilli and bacillus pyocyaneus just as well as with tuberculin, i.e., that such animals were susceptible not only to a specific intoxication because of some abnormal sensitization, but that they were susceptible to other toxic products as well because of their infection. Rumpf concluded that while soluble toxins might be specific and call forth a specific response on the part of the patient, all bacteria probably contained a common component—non-specific—against which immunization might conceivably be carried out. He first made up and used a streptococcus vaccine, but it possessed no therapeutic properties so far as typhoid fever was concerned. It was then that he made up his pyocyaneus vaccine and with it achieved results that in many ways equalled those that Fränkel had obtained with typhoid vaccines. In his series of 30 cases there were two deaths, one from pneumonia, the other from perforation.

Rumpf observed that following his subcutaneous injections chills and sweating were not uncommon. Usually the temperature and the pulse began to come down within two days after commencing the vaccines; the earlier the treatment was commenced the more noticeable the effect on the clinical course. He called attention in particular to the euphoria that was observed after the injection.

This paper, published at a time that witnessed the introduction of diphtheria and tetanus antitoxin, was practically ignored; the more readily when several competent observers, working with small series of cases it is true, could not confirm Rumpf's results.

Then Horbaczewski introduced nucleins and found that lupus vulgaris reacted with a typical focal reaction to the nuclein, that is, the nuclein injection caused a focal reaction about the lesion just as well as the specific substance. Kühne next analyzed the tuberculins and noted the large amount of protein split products therein contained. Koch was cognizant of the fact that the fever-producing element in the tuberculins was not part of the specific effect which he was seeking to accentuate; others (such as Hueppe and Scholl) insisted that it was just this nonspecific bacterial protein that accounted for the entire tuberculin reaction. As a result particularly of Kühne's work, Matthes and Krehl began their well-known experiments with protein split products in tuberculous animals. In using various proteins to bring about the tuberculin reaction in tuberculous guinea pigs they found among others that milk injections would also activate the focus.

In this work Matthes made several observations that have a direct bearing on the problem under consideration. He noted for instance that tuberculous guinea pigs reacted not only to tuberculin with the well-known temperature rise, but to injections of deuterioalbumose as well. With small doses such animals responded with a typical rise in temperature; large doses caused a fall in body temperature and the death of the animal. Nontuberculous animals would at times react with temperature to the deuterioalbumose injection, but never to the same extent as infected animals. The dosage as compared to tuberculin was large, nevertheless the results caused considerable doubt in his own mind as to how far specificity entered into the tuberculin reaction and interested him in the rôle of protein split products in the causation of fever.

To the same period of time belongs the reintroduction of the artificial abscess (the fixation abscess of Fochier), a therapeutic procedure related to the seton and the fontanelle. Fochier used the sterile abscess (produced by injecting turpentine) in puerperal infections with some success. The method was in vogue for a number of years. From Sahli's clinic Bauer published observations on a series of cases of pneumonia treated with such sterile abscess formation (1 to 2 c.c. of turpentine being injected to produce the abscess). The number of cases so treated was too small to be of any particular value but it was noted that a stimulation of leukocytes was always brought about as a result of the injection.

The introduction of nucleic acid by Horbaczewski has been mentioned. In the course of the next twenty years nucleic acid and its salts and related chemical compounds that cause a leukocytic reaction found their way into the treatment of infectious diseases. Their use was advocated because it was assumed that their action consisted in a general tissue stimulation.

Colloidal metals, especially the silver preparations, had come into use after their introduction by Credé. First it was assumed that the

silver preparations possessed particular streptococcidal properties and they were consequently injected in septic conditions due to streptococcus infections. It was then noticed that one could obtain equally good results in a number of infections due to other organisms. Finally the colloidal metals have come to be recognized as purely nonspecific reactive agents.

In the same category must be placed a rather commonly used procedure, the method of autoserotherapy of Gilbert. Introduced in 1894 for the treatment of pleurisy with effusion it found considerable clinical application. The technic consisted in withdrawing a small amount of fluid from the pleural cavity and reinjecting it under the skin. At times a slight temperature reaction was observed following it. Eisner studied the reaction in experimental animals and observed that a leukocytosis usually followed the injection; to this, and to the general constitutional reaction he attributed the therapeutic benefit. Zimmermann had also noted the leukocytosis which he had ascribed to the stimulation of the tissues by autolytic products that had accumulated in the pleural exudate. He even proceeded to show that the injection of peptone would produce such a leukocytosis, but did not continue to the logical conclusion of his experiments. Later the method of autoserotherapy was extended, particularly in the field of dermatology.

In tumor treatment we have had two related measures. These have been the Beard Trypsin treatment of carcinoma and the use of Coley's Fluid, the latter used especially in sarcoma. Quite apart from the theoretic basis that was put forward to support their use in malignant disease, it is to be noted that both agents were followed by a severe constitutional reaction—chill, fever, increased local pain and evidence of an inflammatory reaction, followed by occasional clinical improvement, both in the general health of the patient and the arrest of the tumor growth for a period of time. Whether actual cures were ever effected is for the present study unimportant; both reactions were typical nonspecific phenomena and the effect on the local process just what would be anticipated under the circumstances.

A method closely related to these is that of the injection of tumor autolysates. These are injected either intramuscularly or intravenously in small doses and are almost invariably followed by evidences of a general reaction on the part of the patient (Funkenbein, Blumenthal) as well as by changes in the nitrogen balance (Bauer, Latzel and Wessely).

Another nonspecific method and one that has at times been followed by very favorable clinical results has been that of the injection of leukocytic extracts in patients ill from a variety of infectious diseases. Petterson had observed that in animals such injections seemed to have a very decided protective effect against infection, and Opie, too, had made similar observations. In 1908 Hiss and Zinsser began

to use such an extract in patients. They were not able at the time to account definitely for the therapeutic effect obtained but Zinsser has since expressed the opinion that the results were probably to be accounted for on the basis of a nonspecific reaction.

Occasional clinical reports were made during the period between 1890 and 1910 which detailed success in infectious diseases through a number of therapeutic measures purely nonspecific in character, among them those of Paton, who used normal serum and diphtheria antitoxin in the treatment of tuberculosis, arthritis, and cerebrospinal meningitis.

Paton's work was based on preceding observations made by De Minicis, who had treated a small series of diphtheria cases with diphtheria antitoxin per os, and on those of Lilienthal and of McCallum, who had reported that diphtheria antitoxin possessed curative properties when given in a variety of infections such as sepsis, tuberculosis, adnexal inflammatory conditions, lupus, etc. Paton published a small volume detailing his clinical experience with the use of diphtheria antitoxin given by mouth; he found that not only normal horse serum but sheep serum and ox serum possessed the stimulating qualities to which he attributed the therapeutic effects. This paraspecific serotherapy has been used extensively in France.

Darier has collected some of the clinical literature concerned with the reaction and more recently Cumston has discussed it. That the injection of diphtheria antitoxin might at times produce a transient increase in the temperature of the patient had been observed very early by Ewing, who also noted the leukocytic response after injections, that is, a primary leukopenia lasting for about one-half hour, followed by a leukocytosis. The use of normal horse serum in the treatment of certain alterations of the coagulation balance of the blood has also become quite common in recent years (Weil) and inoculation of the patients serum, plasma or whole blood, either subcutaneously or intravenously—autoserotherapy as it is termed—has been practiced especially by the dermatologists. Within the past five years some success has been reported in this limited field but the method was never recognized as being part and parcel of a general reaction.

In 1917 Deutschmann, seeking to find a method of treatment for certain eye diseases against which remedial measures were unsatisfactory, began the immunization of horses with yeast cells and used the serum for the treatment of a variety of infectious diseases. Yeast has for many years been supposed to augment the resisting powers of the body when given by mouth; yeast extract has also been given subcutaneously for the same purposes and has also been applied in the treatment of malignant diseases (especially by Italian clinicians on the basis of the work of Sanfelice). When so injected the effect is probably due to the nuclein content of the extract.

In Deutschmann's work about 2 c.c. of the serum was injected

and this was followed by the usual nonspecific reaction—a slight rise in temperature, pronounced euphoria, occasional crisis in acute infectious disease, etc.

In America we had, however, one treatment that received considerable unfavorable notoriety, a nonspecific method in its effects, although introduced on a different basis. In 1911 Schafer reported the therapeutic use of a bacterial product with which he had obtained remarkable recoveries in certain infectious diseases.

This work was done at a time when the subject of mixed infections was prominently under discussion as an etiological factor in disease development. Schafer formulated a theory of immunization to fit the successful use of his mixed vaccine. This was that in treating a disease, one had not only to consider the specific exciting organism in the vaccine, but that the secondary invaders—the heterogeneous group of semisaprophytic and saprophytic bacteria that were in symbiotic relation with the original invader—had to be considered in the vaccine as well.

Schafer demonstrated his vaccine mixture in several hospitals, treating chiefly arthritic cases. The injection, usually made intravenously because subcutaneous injections were very painful, was always followed by a severe general reaction, no matter whether the therapeutic result was good or bad. In some cases the success following the single injection was remarkable; in others, merely the memory of the very unpleasant chill and fever—"the Ordeal by Chill and Fire" as one facetious patient expressed it—remained, with no therapeutic benefit. The selfsame vaccine in one case cured arthritis, in another a catarrhal jaundice, in another a neuralgia. At this time a pharmaceutical house purchased Schafer's formula and began a country-wide exploitation of the same, using a trade name for the product. The entire campaign, naturally enough, met with decided disapproval on the part of the medical profession, not only because of the proprietary nature of the product and the blatant commercial method of its introduction, but because of the lack of scientific or laboratory study that was evident from the very beginning.

Herescu and Strominger attacked the problem from a different position. Noting the morphological similarity that exists between the gonococcus and the meningococcus, they began using antimeningococcus serum in the treatment of gonorrheal arthritis, gonorrheal ophthalmia, septicemia, and other gonorrheal complications, with considerable success.

The use of mixed gonococcus vaccines had become quite common both in France and in Germany and in their clinical application a number of observers began to use them intravenously in relatively large doses. In the gonorrheal complications (and in iritis of non-gonorrheal origin—Kreibich) it was found that this form of injection was frequently satisfactory. Brasch, who studied the general re-

action that followed the injections, noted in particular the typical effect on the leukocytic picture.

We have then a whole list of agents and methods that have been employed, some empirically, others with a definite immunological theory underlying their use, but all, whether bacteriological product, or enzyme, or chemical, producing a more or less marked constitutional reaction on the part of the patient. It is curious that this common feature was not emphasized or even recognized as a possible part of the therapeutic mechanism.

Throughout the period under discussion, when these various methods and substances were being introduced, vaccinotherapy as advocated by Wright was being tried out in practically every form of infection; not always with success but with sufficient result to keep the method in use in medical practice.

When failure resulted there were, as a rule, extenuating circumstances upon which to throw the blame. At first it had been the practice to use as a vaccine an organism of the type known to cause the particular infection with which we were dealing. Then when results were not forthcoming, effort was made to isolate the particular organism causing the infection in order to produce an autogenous vaccine. This failing, we had the consolation that we probably had not succeeded in isolating the particular strain that had caused the infection.

On the basis of his opsonic work Wright had differentiated a negative and a positive phase of resistance following the vaccine injection. The dread of the negative phase was sufficiently impressed on every immunologist to prevent the use of large doses of vaccine or such that would lead to a general reaction on the part of the patient. Indeed, ever since the time of Koch's work with tuberculin, when overzealous workers using large doses of tuberculin had often done irreparable damage by breaking down the normal connective tissue defense of the patient, immunologists had used great care in avoiding general systemic reactions.

When vaccines were carefully used there was no doubt that the patient gave evidence of increased antibody production, measured both by the opsonic index, the agglutinin titer and the method of complement deviation, but here again the therapeutic result did not measure up to the expectation. Immune bodies might be stimulated to a sufficient degree but the patient was not cured.

The modern conception of protein therapy and nonspecific resistance was a direct development, however, of this work with vaccines. In typhoid fever the therapeutic use of vaccines, either made up of killed but otherwise unaltered organisms, or of bacteria altered in a number of ways, had been given rather extended use and with fair clinical results. In the decade following the year 1906, the bacteriotherapy of typhoid began to be a recognized procedure. The dura-

tion of the disease was undoubtedly shortened thereby and the mortality lowered, but the difference between the treated and the untreated cases was seldom striking enough to popularize the method among the general profession. Then it was that in Argentine a group of physicians began the intravenous use of typhoid vaccine. Penna, Tores, Dessy, Grafinoia, Fossati, and others thereby obtained quite remarkable results, the disease in some cases being aborted almost at its inception, in others terminated by crisis, in others by lysis shortly after the injection.

Kraus, who was working in Argentine, heard of these results and after observing the effects investigated whether other organisms would not produce the same results when so injected. He found this to be true with colon vaccine.

Quite independently Ichikawa had reported on the advantage of the intravenous injection of typhoid vaccine at a meeting of the Medical Society of Osaka in April, 1912, and in 1914 reported his results with 87 cases of typhoid treated with a sensitized vaccine. The normal mortality in his untreated cases was over 30%; when treated with the vaccine intravenously the mortality sank to 11% and in more than half the cases the disease was terminated after the first or second injection. Ichikawa made the further interesting observation that when he treated paratyphoid fever with the same typhoid vaccine, he obtained equally good results, i.e., the result was not due to a strictly specific reaction. Ichikawa found that following the typhoid injections in the paratyphoid patients, the specific paratyphoid antibodies were mobilized.

Some hemorrhages were noted after the injections, although the author considered them less frequent in the vaccinated group than in the unvaccinated. Heart disease and pregnancy he naturally considered contraindications to the therapeutic injections because of the pronounced reaction that followed the administration of intravenous therapy.

We had then two reports of heterobacteriotherapy that had yielded startling clinical results—typhoid treated with colon bacilli and paratyphoid treated with typhoid vaccine—clinical results that could not well be denied, although the immunologist might still allege that we were dealing with a group reaction, rather than a true heterobacterial vaccine effect.

Kraus, however, definitely settled this point when he reported favorable results in puerperal infection treated with colon vaccine and with this as a basis began the treatment of scarlet fever, plague and septicemia.

A predecessor of Kraus and perhaps the first observer who clearly pointed out the value of heterobacteriotherapy was Renaud (1911). He had been working with typhoid vaccine killed by quartz light radiation and noted that the injection of such vaccine had a definite

therapeutic effect on a number of inflammatory conditions of nontyphoidal origin.

Clinical results such as those reported by Renaud, by Kraus and by Ichikawa were not to be explained away as due to accident. The conception of strict specificity in therapeutics that had been built up in the laboratory had to give way before a clinical demonstration that could no longer be ignored. Our recognition of nonspecific therapy really had its inception with these three papers. Nor was it long before a series of corroborative observations appeared in the European literature from a number of clinics and in a number of diseases. Many clinical phenomena heretofore obscure and never satisfactorily accounted for on our older conception of immunity began to appear relatively simple and understandable when studied from the new point of view.

From heterobacteriotherapy it was but a logical step to attempt the intravenous injection of bacterial components and bacterial split products, then to protein split products of nonbacterial origin and finally to the realization that any substance which was capable of inducing the shock reaction on the part of the patient would result in general in the same therapeutic change. We were dealing with an ergotropic as von Gröer termed the reaction—"eine Umstimmung"—of the whole organism (analogous to our term desensitization) which made it resistant to intoxication. Soon a number of agents were so used. Schmidt and Saxl introduced milk injections, Lüdke the injection of proteoses or albumoses, Mittländer the use of hypertonic salt solution. Distilled water and foreign sera were next added and recently the ancient method of producing sterile abscesses—by injecting minute doses of turpentine and hypertonic salt solution—has been revived.

It was recognized, too, that some of the older substances, such as nucleic acid, colloidal metals, enzymes, lipoids and a long list of substances, the therapeutic effect of which had been variously explained, all belonged in the same category. When reviewed from this point of view it became evident that they all brought about a general reaction which manifested itself as a rule in the chill, the fever and the leukocytosis, and those which were most successful clinically were the ones following the use of which the reaction was greatest. It had also been the common experience with the entire group that in order to be effective they had to be given early in the disease; when used late the effect was much less certain.

In view of the undeniably striking therapeutic results at times achieved with nonspecific therapy certain enthusiastic workers immediately went to the extreme view that specificity was valueless in therapeutics and were ready to throw overboard the accumulated results of the past thirty years. And the best known and most widely used of our specific agents, diphtheria antitoxin, was the one that was

first brought into question. Bingel treated about 1,000 cases of diphtheria, one-half of the group with the specific antitoxin, the other half with "empty," i.e., normal horse serum. According to his report the clinical results were equally satisfactory in both series. Subsequently a number of German clinicians went over his results but could not confirm them to the extent that Bingel had claimed. One point of value was, however, brought to our attention by this discussion of the antitoxin question. Along with the specific antitoxin value the serum contained a nonspecific stimulating element in the horse serum protein. Our modern highly concentrated sera naturally have lost this nonspecific factor to a considerable degree in the process of concentration, thus justifying the criticism that has repeatedly found expression in recent years, that the modern concentrated serum did not seem so effective, all things considered, as the old serum which was not so high in antitoxin units. Concentrated antitoxin contains less of the nonspecific factor; whatever may have been the clinical value of this element has been lost in the modern preparations. (Meyer.)

This recognition of dualism in the therapeutic effect, the specific antitoxic factor and the nonspecific stimulating factor of the diphtheria antitoxin merely illustrates the importance of the unbiased study of all factors in therapy.

We are fairly well grounded in our knowledge of the specific factors of immunity. Our knowledge of the nonspecific elements is still decidedly fragmentary. Enthusiasm in one direction should not for an instant obscure our vision of all other possible factors in resistance.

Here in America interest in this particular phase of resistance was stimulated by the work of Vaughan and Wheeler, of Opie and his associates and later by that of Jobling and his co-workers.

During the course of these latter studies we had under observation a series of animals intoxicated with a variety of bacterial and other protein substances and noted in these animals a marked mobilization of serum enzymes. When we became familiar with the work of Kraus and Ichikawa we studied the problem from the point of view of its practical application and concluded that at least part of the therapeutic effect must be due to enzyme action. Inasmuch as we had previously found that other agents besides bacterial vaccines would produce precisely the same enzyme mobilization we concluded to try a series of protein split products in patients ill with typhoid fever. While this work was under way an identical investigation carried out by Lüdke with albumoses came to our knowledge, delayed of course by the exigencies of the war. Miller and Lusk had in the meantime also become interested in this form of therapy and were the first in this country to report a larger series of cases so treated. They used both typhoid vaccine and secondary proteoses in their work. Smith in a paper published at the same time reported on the therapeutic bene-

fit of the anaphylactic shock reaction in patients suffering from gonorrhoeal complications.

The publication of these papers directed the attention of the American profession to this form of therapy and there have since appeared a number of reports dealing with nonspecific therapy in a variety of diseases. These will be discussed in detail.

## CHAPTER II

### THE NONSPECIFIC AGENTS

In the practice of nonspecific therapy a large number of therapeutic agents have been used, varying from the ancient forms of counter-irritation to our present methods of heterobacteriotherapy, of protein therapy and of the intravenous injection of colloidal metals or other colloidal substances. In discussing these various agents that we have at our disposal to induce the "plasmaactivation" or the "ergotropic" as one may choose to term the reaction, it will be of some interest to include a number because of their historic association or because of their theoretic rather than their practical therapeutic value. Their inclusion is therefore not to be regarded as an endorsement of their usefulness in therapeutics nor as an advocacy for their employment in practice. They are gathered together under a single group because it seems most probable that their occasional utility—and of this there can be no question in some instances—seems based on a similar reaction that they bring about in the body, i.e., true tissue stimulation and activation, exercising their therapeutic power by altering the reactivity of the whole organism, rather than influencing directly the cause of the pathological process. The following list, extensive though it is, is by no means complete. The various drugs that possibly are useful because of a similar stimulation—among them some of the mercury preparations; cinnamic and succinic acids and their salts, formic acid, quinin, the antipyretics, iodine, etc.,—have not been included because it would lead the discussion too far afield. A large number of other and older methods that at some time in history have been used in medicine and which probably had as the basis of their usefulness the same general reaction, have also been omitted because a discussion of them, other than emphasizing the historical continuity of their employment as nonspecific agents in therapeutics, would have no value.

#### THE NONSPECIFIC AGENTS

##### COUNTERIRRITANTS

Cautery      Seton      Fontanelle      Moxa      Blister      Rubefacient

##### BLOOD AND SERUMS

*Normal*—Human, Horse, Sheep, Beef, Goat, Chicken, etc.

*Immune*—Human Convalescent Serum; Antimeningococcus Serum, Antidysentery Serum, Antistreptococcus Serum.

Diphtheria and Tetanus Antitoxin.  
Antiyeast Serum (Deutschmann Serum).

Tuberculosis Serum (Marmorek, Maragliano, etc.).

*Related Agents*—Plasma Serum (Richet), Blister Serum, Pleural Fluid,  
Cerebrospinal Fluid.

#### PROTEINS

Egg Albumin and Seralbumin    Milk    Fat-free Milk    Casein    Gelatin

*Plant Proteins*—Nucleoproteins—Nucleohexyl

#### *Protein Split Products*

Proteoses    Deutero-albumose    Histamin    Globin    Witte Peptone

#### *Enzymes*

Trypsin    Amylopsin    Leukoprotease (Leukocytic Extracts)

#### *Tissue Extracts*

Tumor Autolysates and Extracts    Cartilage and Vascular Extracts  
(Heilner)

#### Organotherapy

#### *Vaccines*

Typhoid, Dysentery, Colon and Cholera Vaccines. Meningococcus and  
Gonococcus Vaccines. Staphylococcus, Streptococcus, Pyocyanus  
and Pneumococcus Vaccines. Influenza, and Diphtheroid Vac-  
cines, etc.

*Mixed Vaccines*—Vaccinurin. Danysz' Method. Much's Antigen.

#### BACTERIAL EXTRACTS AND RELATED PRODUCTS

Tuberculin    Typhin    Coley's Fluid    Phylacogens    Bacterial Autolysates

#### COLLOIDAL METALS

Gold    Silver    Manganese    Platinum    Sulphur    Mercury    Zinc    Iron

#### MISCELLANEOUS

Hypertonic and Hypotonic Salt Solutions    Sugar Solutions    Distilled Water  
Formalin    Solusin    Hetol    Iodids    Turpentine    Antipyretics

#### Yeasts

*Irradiation*—Sunlight    Roentgen Rays    Radium

Biological Alterations

Depression Immunity

## COUNTERIRRITATION

(*Thermocautery, Seton, Fontanelle, Moxa, Blisters, Rubefacients*)

These, perhaps the most ancient of our methods of intervention in disease processes, purely empirical in origin, represent undoubtedly a form of nonspecific therapy. Crude and barbarous in their application though some were, there can be little doubt as to their occasional efficacy. Their very antiquity, their widespread use among all peoples and their long continuance in practice more than warrant this assumption. And their supposed effects on inflammation—the acceleration of repair—relief from pain—hastening of absorption of exudates, might be expected to follow as a result of nonspecific protein therapy as we now understand it.

Every one of these procedures has as its basis the production of a focus either of necrosis—such as produced by the cautery; of suppuration—as with the use of the seton or the fontanelle; or in the milder forms the production of an area of exudation, inflammatory in character, usually serous or seropurulent. The absorption of these pathological exudates by the body must lead to a tissue stimulation—perhaps milder in degree and longer in duration—similar to that which follows in the wake of our more modern nonspecific therapeutic injection. Bloch was one of the first to call attention to the fact that our nonspecific therapy is but part and parcel of this older practice of counterirritation.

While counterirritation was, as a rule, limited in its application to localized inflammation and seldom if ever used in acute infectious diseases, we do find that it was recommended in inflammatory rheumatism, curiously enough the one disease in which modern nonspecific therapy has perhaps been most consistently successful.

*The Actual Cautery* was considered the most effectual agent. We now know that following a burn the resorption of necrotic material from the burned area may result in a typical protein shock reaction, either acute or protracted, depending of course on the degree and the area of injury. Pfeiffer has recently studied in detail the flooding of the organism with proteolytic enzymes following both burns and evitable infection of such issues.

The *Seton*, the *Fontanelle*, and *Moxa* were all methods designed to produce a superficial suppuration over a longer period of time. Not only were necrotic tissue products being absorbed from such foci, but a heterovaccination carried out at the same time because of the inevitable infection of such tissues.

The milder methods produced merely local irritation of the skin either with vesication or hyperemia; absorption of a slight inflammatory exudate might take place from both. In all of these pro-

cedures, differing but in degree, we have the elements of the modern nonspecific therapy, the absorption of a foreign protein (disintegrating autogenous material—either burned tissue, disintegrating leukocytes, fibrin or serum from an exudate)—the reaction of the body to this material with increased activity; stimulation of the bone marrow; mobilization of leukocytes, of enzymes; the lessening of the nervous irritability, etc.

Counterirritation was, however, limited in its application to localized inflammatory conditions, differing in so far from the application of the nonspecific methods at present in vogue.

Calleja has but recently devised a method of therapy which he considers an immunization against necrosis based essentially on these older methods. Calleja assumes that the derivatives of empiric medicine, the blisters, the fixation abscess, etc., owe their efficacy to the fact that they induce an active and a passive immunization against the effects of the necrosis of the tissues in the disease process. Subcutaneous injection of 3 or 4 drops of chloroform at different points, to a total of from 3 to 5 c.c., is a convenient method of this "causticotherapy," and he supplements it with horse serum prepared like diphtheria antitoxin, only using instead of diphtheria bacilli, human tissue scraps rendered necrotic with chloroform.

The term "counterirritation" and the theories advanced to explain the therapeutic measure in the treatment of disease have gone out of fashion, together with the agents that were used for many years. At times and under certain undetermined conditions results were achieved by means of counterirritant measures that were quite satisfactory. But counterirritation was a therapeutic measure absolutely empirical in character and the fact that no possible theory of modern medicine could account for its potential benefit was perhaps one of the reasons that modern medicine discarded the practice. As Gillies has expressed it, "The remedy, or let us say mode of treatment, fell into disrepute not because it failed as a remedy or as a mode of treatment, but for the very peculiar reason that we do not understand and cannot explain how it succeeds, for it is allowed that not infrequently it does succeed." Curiously enough we continued to elaborate procedures that were obviously similar to counterirritation both in character and in their therapeutic object, but under a variety of new names and based on modern scientific theories of immunity. So, for instance, the autoserotherapy used in pleural exudates whereby a small amount of the pleural exudate is withdrawn and reinjected under the skin of the patient, in mechanism analogous to the older form of vesication.

It was not, however, until within the last few years that the possibility was suggested by observers interested in nonspecific therapy that the same mechanism that was concerned in the one was possibly involved in the other; Luithlen has even ascribed the possible thera-

peutic effects of repeated bloodletting to biological alterations related to protein therapy.

#### BLOOD, SERUMS AND RELATED AGENTS

**Blood Transfusion.**—One of the very early methods of nonspecific therapy involved the transfusion of whole blood from human or animal sources; with the method a reaction on the part of the patient was a common observation. It was this reaction that made the method dangerous, because it could not be controlled and yet it seems to have been recognized that in its occurrence lay the usefulness of the method as a therapeutic measure. Hasse used sheep's blood in the treatment of a large number of diseases (1874) and Eckert (1876) definitely recognized that the injected or transfused blood did not act as a substitute but as a chemical irritant for the organism which had received the injection. Bier made similar observations and while at times certain clinical improvement followed these earlier attempts the methods never came into prominence because of obvious limitations. In the modern use of transfusion we are dealing only with the effort at substituting or making good a serious loss of serum or corpuscles and every effort is made to avoid a reaction on the part of the recipient.

**Normal Human Serum.**—*Autoserotherapy.*—The use of *normal human serum*, drawn from another individual or from the patient (autoserotherapy) for either subcutaneous or intravenous reinjection, is not a new procedure. The use of normal serum in hemorrhagic diathesis in particular has been in vogue a number of years. (Weil, 1908.) It is probable that in the mechanism of clotting a colloidal rearrangement of sufficient magnitude is brought about so that the serum becomes toxic for the homologous organism, and that it is this change which accounts for the fact that the serum brings about a general reaction.

Serum when first defibrinated is decidedly toxic to the homologous animal, a fact that should be kept in mind in judging the reaction elicited. Freund in studying this question noted that when defibrinated blood was injected in experimental animals within 15 minutes after drawing the same, death followed very promptly; if a little more time elapsed the animal went into collapse; if injected within 30 minutes the animal reacted with fever. From this time on the serum, up to 20 hours after preparation, produced merely a very slight febrile disturbance.

In recent years a number of interesting papers have been published dealing with the injection of homologous serum, especially in the hemorrhagic diseases. In the American literature, too, the method is very favorably reported. (Freeman, Huber, MacFarlane, Kaiser, Sophian, Hartmann, Belliboni, Rosenberger, LeClainche and Vallee, Jousset, Mosti, Rosler, etc.)

In using *autoserotherapy* blood is drawn from a vein of the patient and this is permitted to clot—or may be defibrinated. The

serum drawn from the clot (or after centrifuging the defibrinated blood) is reinjected intravenously, usually once or twice during the course of the week. Little or no reaction follows the procedure and the therapeutic success is not very brilliant, considering the amount of time consumed with the manipulation. Perry substituted horse serum with seemingly good results.

**Normal Animal Serum.**—Horse serum, beef serum, goat serum, sheep serum, chicken serum, to mention but a few that have been used, were first injected subcutaneously, in more recent years intravenously; the dosage that can be used with safety varies with the serum, its age, method of preparation, whether preservatives have been added and the sensitization of the patient. As much as 250 c.c. of beef serum have been given intravenously (in anthrax) without injury; indeed the larger doses have in most cases been more satisfactory than the smaller ones. The reaction to these serums is as a rule very mild, only occasionally is a fever and chill observed. Before injecting serums of this type a skin test should be made to determine whether the patient is possibly sensitive to the serum the use of which is contemplated. With repeated doses the reaction, contrary to the result with many of the other nonspecific agents, may become more severe, even when the injections are made within the time period usually allotted before active sensitization will occur. Intravenous injections must always be made very slowly even when there is no evidence of sensitization. If the patient has become sensitive great caution must be observed, although Smith has made use of the fact that patients become sensitized to serum injections, for therapeutic results. He found that when patients became sensitive to serum injection and reacted with some temperature increase and a general systemic reaction, a definite curative effect was to be observed on local inflammatory conditions (gonorrhoeal complications). Normal serum was recommended for injection in cases of diphtheria by Bertin as early as 1895.

**Immune Serum.**—The use of the serum of *convalescent patients* for injection either subcutaneously or intravenously is a procedure that also dates back for a considerable time. It was used in typhoid fever with some success but the most extensive application has possibly been in the treatment of scarlet fever, and more recently in the treatment of influenza. To be used successfully large doses must be employed and the treatment given early, two facts that suggest very strongly that the effect is due less to any antitoxic or antibacterial property of the serum, than to the nonspecific stimulating effect of the serum proteins.

Weisbecker had used subcutaneous injections of convalescent serum in scarlet fever in 1897, but the method was not extensively used until Reiss and Jungmann emphasized the value of the treatment with larger doses. From 80 to 100 c.c. of serum are now commonly em-

ployed, being injected intravenously whenever practical. Rehder bases his dosage on the body weight, injecting 2 c.c. of serum per kilo. Very little attention has therefore been paid to the determination of the isoagglutinins that may be present in the serum injected intravenously and at times rather severe reactions have been reported (Griesbach), probably because of the neglect of this precaution. Of course the serum used should be tested by means of the Wassermann reaction before injection.

**Antibacterial Serums and Antitoxins.**—*Antitoxins* of various kinds and *Antibacterial Serums* have been widely used, these including diphtheria and tetanus antitoxin, antistreptococcus, antipneumococcus, anti-dysentery serum, etc. This paraspecific serum therapy, as it is commonly termed, has found extended use both in France and England, and to some extent in this country. Such serums are not only used for injection—(intravenous, intramuscular and subcutaneous)—but have been given orally. Paton in his “New Serum Therapy” discusses this method and the results obtained therewith.

“In 1895 Bokenham had observed that the administration of diphtheria antitoxin seemed effective against streptococcus infection; De Minicis the following year administered diphtheria antitoxin orally in five patients with good results; in 1897 Lilienthal observed the efficacy of Streptococcus Serum in a variety of surgical conditions, while McCallum tried injections of diphtheria antitoxin in tuberculosis, lupus and adnexal inflammations with good results.

“On this basis Paton began his work, using antitoxins as well as sheep, horse, and beef serum interchangeably in a large series of cases and various diseases, with at times very interesting results.

“Darier took up this study in France and quotes a considerable literature dealing with therapy of this kind.

“In pneumonia Talamon in 1901 treated about 115 cases with considerable success with diphtheria antitoxin; Mongour used it in bronchopneumonia and pulmonary abscesses and Launois also treated several cases. Deronet and Jeulin applied the treatment in 31 cases of pleurisy; their favorable report was confirmed by Faure in a small series of cases. Burkard used serum in the treatment of exophthalmic goiter and Bloch obtained good results using tetanus antitoxin. Weil reported on the use of such sera in hemophilia as well as in peritonitis, sepsis, puerperal infection, etc. Freund in 1911 tried normal horse serum in the toxemia of pregnancy. In typhoid Mongour and Cazamin, Marotte and Oui used diphtheria antitoxin; Albert Levy used it in dysentery. In arthritis L. Ramond and Chiray, Passavy and Chauvet and Guithard reported excellent results. Iritis was treated by the same means and in erysipelas Launois, Apostolleum, Polak and Mayweg reported good results.”

Cumston has but recently called attention to the fact that in France paraspecific therapy has been commonly employed both in the army and in civilian practice, particularly in ocular infections. Diphtheria antitoxin is usually used for oral administration in military

practice but where the conditions are favorable the subcutaneous and intravenous use is preferred. It is said to relieve pain and induce a pronounced euphoria.

The dosage, as may be expected, is not a fixed one. The serums are in this case given not for their antitoxic property but for their nonspecific stimulating effect. A very small dose in a sensitive patient may be sufficient to induce a severe reaction; usually however the dose may be fairly large after a careful determination has been made as to the degree of sensitization of the patient. The agents of this type have the advantage that they can be obtained in sterile containers ready for administration. They do not as a rule give any striking therapeutic results such as one may observe from the more toxic agents but offer a relatively safe means of experimentation until the physician becomes more or less familiar with therapy of this type.

**Deutschmann Serum.**—The general increase in resistance to infection that is observed after the use of yeast led Deutschmann in 1907 to try out a novel method of this principle. He immunized horses with yeasts for a considerable period of time and then used the serum in a number of diseases. He was interested chiefly in eye diseases, but the serum was tried out in a variety of acute infections as well. He had observed that his yeast-immunized animals all became more resistant to general infection, and believed that this change in resistance was due to a serum alteration.

The serum was injected into patients both subcutaneously and intravenously, but in relatively small dosage,—from 2 to 4 c.c. In his series of cases there were 24 pneumonias treated with the serum, of whom three died. In four of the cases a crisis was observed immediately after the injection. In all of the cases the euphoria following the injection was well marked. The serum has been used in general sepsis, erysipelas, various inflammatory conditions,—furunculosis, otitis media, impetigo, eczema,—and with seemingly good results in eye conditions—traumatic inflammation—hypopyon keratitis, iridocyclitis, iritis, etc. (Bockhoff.)

In lupus vulgaris a marked local inflammatory reaction was observed as with all other similar nonspecific agents.

**Tuberculosis Serum.**—The commonly used preparations of Maragliano and of Marmorek cause reactions in tuberculous patients that have been ascribed to various immunological alterations but are very probably due to their action as nonspecific proteins. The temperature is increased after injection, focal reactions take place, there is an increase in the amount of sputum, etc. Just as with other nonspecific agents used in the treatment of tuberculosis, incipient cases are frequently benefited, advanced cases on the other hand are unfavorably influenced.

**Related Agents.**—*Plasma Serum* has been used particularly by French observers. Grigant and Montier have used the method in the

treatment of influenza. Rabbit plasma is mixed with human serum and injections of this mixture are given intravenously.

*Blister Serum*, an infrequently used method, consists in producing a local vesicle in some area of the skin, withdrawing the fluid transudate and reinjecting the same. It possesses no properties of unusual activity.

*Pleural Transudates and Exudates* (also termed autoserotherapy).

Gilbert at the Medical Congress at Rome in 1894 reported that he had successfully treated pleuritic effusions by withdrawing a limited amount of fluid from the chest and reinjecting the same under the skin of the patient. The resorption of the pleural exudate was said to be greatly hastened. A long list of clinicians soon published reports with the method, most of them with favorable results—Fedde, Gerouzi, Tchigaoff, Nasseti, Marcon, Durand, Schnütgen, Duncan, Modinos, Indelli, Fiori, Landmann, Linser, Spiethoff, St. Mello—a summary of the work having been collected in a review by Fishberg.

The technique is very simple; 5 to 10 c.c. of fluid are withdrawn from the chest on alternate days or at longer intervals and reinjected subcutaneously without withdrawing the needle to the surface of the skin. In some instances a very slight temperature rise has been noted to follow the injections; in most cases, however, no reaction follows. Zimmermann studied the mechanism involved and observed that a leukocytosis followed the injection. He was of the opinion that the reaction was due to autolytic products of tissue degeneration that were contained in the pleural fluid and made the observation that when he injected such products of tissue destruction—peptones—in animals, a leukocytosis resulted. Eisner also observed this leukocytosis.

Lyter has recently gone over the subject and has come to the conclusion that the injections of pleural fluid have little or no influence in hastening the absorption of the exudate. In 23 cases carefully followed, treated by withdrawing 5 c.c. of fluid daily and reinjecting the same, 8 were completely reabsorbed in two weeks' time—34%, while in the balance the effusion did not lessen as a result of the treatment. Lyter observed practically no leukocytosis and in only two of the 8 rapidly resorbing cases did he observe any temperature reaction at all.

It seems probable that the method is at best a very mild stimulant of resorption because the nonspecific response is practically negligible as far as the effect on temperature and leukocytosis is concerned. Perkins has recently modified the procedure somewhat in that he draws a larger amount of fluid from several patients, pools the samples and adds the same to citrated saline solution. To this a 5% solution of carbolic acid is added (to 10% of the total volume). Of this mixture he begins injections of from 1 to 2 c.c. subcutaneously, gradually increasing the dose until he gives from 10 to 25 c.c.

**Cerebrospinal Fluid.**—v. Zielinski has published results obtained in the treatment of typhus fever with subcutaneous and intravenous injections of cerebrospinal fluid drawn from the patient. The dose was usually 15 c.c. and he claims to have obtained good results from such injections.

**Joint Fluid.**—Dufour and Debray announce that the fluid from a gonococcus process in a joint answers all the requirements for an efficient and harmless autogenous vaccine when injected subcutaneously. There is no need to heat or sterilize the fluid; they injected it under the skin of the thigh, and state that the general symptoms, and the general and localized pain rapidly subsided, and the temperature gradually declined in their three cases. The effect on the urethral and vaginal processes could not be determined as local measures had been tried there as usual.

**The Local Effects of Serum, of Normal Salt Solution and of Iodid Injections.**—The treatment of wounds and of local tissue inflammation by means of local injections of serum, homologous as well as foreign, is a more recent development. Müller has discussed the effect and the possibilities and Wright in his studies on local tissue resistance to infection has also made use of this method. When so employed in cellular inflammation the injection is followed by marked amelioration of the local symptoms, pain, tension and swelling being markedly diminished. The local injection of physiological salt solution is said to be followed by a similar analgesia. The method has been most extensively employed in the treatment of gonorrhoeal complications, especially epididymitis.

As a rule 10 c.c. of serum or salt solution are injected into the scrotum near the site of the inflammation.

These methods are related to Bier's method of treatment by passive hyperemia. As a matter of fact Bier has called attention to the effect of foreign protein injections in infectious diseases in a very early paper and has always been an advocate of related measures.

#### NATIVE PROTEINS

Von den Velden seems to have been one of the first to have used native protein injections in therapy with the distinct thought underlying this procedure that he was thereby stimulating certain nonspecific fermentative reactions in the body which would be useful in increasing the general resistance to disease. He found for instance that the vasomotor activity around the local pathological area was increased, that there was evidently an increase in the lymph flow, of the leukocytic reaction, etc.

**Ovalbumin and Seralbumin.**—Von der Velden at first used solutions of ovalbumin and seralbumin in 5% and 10% solution. This he

injected subcutaneously in doses of from 5 to 10 c.c.; later he used intramuscular and intravenous injections.

Holler has also used ovalbumin. The general reaction is negligible and the therapeutic effect not striking.

**Milk.**—The intramuscular injection of milk was introduced by Schmidt and by Saxl in 1916 to induce a protein reaction, i. e., the typical rise in temperature observed following other agents. Milk offered the advantage that it would be easily available to the profession. The method is very simple. Ordinary pasteurized (or fresh) milk is boiled for from 5 to 10 minutes and when cooled, from 5 to 10 c.c. are injected intragluteally, or into other muscles—arm, back, etc.

The injection is followed in some instances by a chill (not as severe as that following typhoid vaccine), and by a temperature rise that reaches its maximum in from 6 to 8 hours and then subsides within 24 hours. A well marked leukocytosis, ranging from 15,000 to 40,000, also results. Milk has a decided styptic effect when so injected and as Doellken has shown is of particular value in diseases associated with hemorrhages. This effect is probably due to its effect on the liver parenchyma, which, together with the bone marrow, seems to be especially stimulated by the milk injections. Thrombokinase and fibrinogen appear in increased amounts in the serum after injection. Locally there may be considerable pain at the site of the injection.

Milk being composed of many and varying elements, efforts have been made to identify those components that might be most efficacious. The bacterial content in particular has been held responsible for the reaction produced by the milk injection. Indeed Bessau, Decastello and E. F. Mueller believe that the reaction is due wholly to the bacteria that are contained in the milk, and Uddgren found that the reaction following sterile milk injections was relatively mild in character. She has determined that commercial milk, even after boiling for from three to five minutes, may still contain a few viable organisms. Boiled for ten minutes the milk was always found to be sterile. Uddgren believes the reaction of the milk is due to bacterial derivatives or protein split products contained in the milk.

Ryhmer, who obtained rather unsatisfactory results with milk injections—he tried it in diphtheria carriers, in hemorrhage, in anemia, osteomyelitis, sepsis and Barlow's disease—also believes that the reaction is due wholly to the bacteria contained in the milk because with fresh sterile milk he obtained practically no reaction.

When repeated injections of milk are given the reaction of the patient may increase to some extent, differing in this manner from the effect of reinjection when bacteria and proteoses are used. There seems to be relatively little danger of sensitization or of anaphylactic shock following repeated milk injections; many thousand injections have

been reported and but few cases of shock following the repeated injections (Sachs, Oppenheim, Lubliner, van Randenborgh). The last observer is of the opinion that some of the milk preparations (caseosan, etc.) are more apt to be followed by shock symptoms than are milk injections.

Where shock symptoms have occurred it is by no means excluded that part of the injection may not have accidentally reached a vein. Great care should always be exercised that the injections are intramuscular.

The fact that there is relatively very little sensitization of the patient following milk injections has been variously accounted for. The human organism is not, as a matter of fact, very susceptible to anaphylactic shock under any circumstances, and Salus has suggested that in the case of the milk injections the fact that the milk has been boiled would tend to dedifferentiate it and diminish the tendency to sensitization.

Slawik recommends the use of *human milk* in place of cow's milk, especially in the treatment of infants. He found that both wet-nurses and atreptic infants were refractory to such injections, there being absolutely no temperature response. According to Epstein adults react to human milk with an increase in temperature, etc., just as they do to cow's milk.

*Local injections* of milk have been used by Weiss and others in the treatment of buboes and local inflammatory processes. While a general reaction results, there is a decided local effect similar to that noted when serum and physiological salt solution are injected locally. (Vide.)

For intravenous injection *fat-free milk* has been prepared by thoroughly extracting the milk with fat solvents and later carefully evaporating the solvent that may, after gross separation, still be present in the milk.

**Casein (Aolan, Caseosan).**—Lindig and Müller both proceeded to refine this so-called "milk therapy" by using purified casein in its place. This has the advantage of being a chemically constant product, free from bacteria, for which one might presumably determine a standard dosage.

Lindig has used a 5% solution. This is prepared by adding 5 grams of purified casein to a N-10 solution of sodium bicarbonate (20 c.c.), shaking and agitating the same until the casein is all dissolved and then adding 80 c.c. of distilled water. Of this solution from  $\frac{1}{2}$  to 1 c.c. is given intravenously. Injections are followed as a rule by a chill in about 1 hour, some headache and a moderate increase in temperature—about 3° F.

Müller has used a similar casein preparation which has recently been placed on the European market under the trade name of Aolan. While Lindig considers that the casein represents the active substance

that is responsible for the reaction that follows milk injections, Müller is of the opinion that the casein, just as the milk itself, represents merely a foreign body and that the other constituents of the milk will also give a similar reaction.

A similar preparation—Caseosan—has also been recently placed on the market. Both are merely solutions of casein in sterile containers.

Casein occupies a rather unusual position among the native proteins because of the rapidity with which it is split and particularly because it is hydrolyzed by erepsin; the latter fact would make the splitting of the injected casein probable in almost any of the tissue fluids. Riedel calls attention to the fact that the mono- and diamines derived from the casein would act as powerful activators for tissue activity and, as a result, for enzyme activity.

**Gelatin.**—The use of gelatin for intravenous injections was recommended a number of years ago because it was assumed that the gelatin would be much more efficacious in retaining water in the vascular bed in cases of shock and after severe hemorrhage, as the gelatin forms a hydrosol. The injections were at times followed by evidences of a nonspecific reaction of mild degree—chill, sweating, and febrile rise. Clark has recently studied the reaction of rabbits to such injection. The possibility that tetanus may follow injections of gelatin, especially when given subcutaneously, must be kept in mind. (Weber.)

**Plant Proteins.**—Münch has reported on the use of plant “press-saft” for parenteral injections. In this country a number of such agents, of unknown origin or composition, supposedly derived from plants, are on the market and are exploited under proprietary names. A rather amusing inconsistency is to be noted in that these nonspecific proprietary agents are prepared for specific purposes, that is for each disease there is recommended a specific “nonspecific” agent.

**Nucleic Acid and the Nucleins.**—Nucleic acid was first brought to the attention of the scientific world at a meeting of the *Basel Naturforscher Gesellschaft* in 1874 when Miescher discussed its chemistry. It was not, however, until almost twenty years later that Horbaczewski introduced it into medical practice and observed its leukocytic stimulative properties. Maurek shortly after reported on the effect of subcutaneous injections on the leukocytic picture and on the temperature curve, and Netter introduced it in France. It was soon extensively used in a number of infectious diseases and in a variety of degenerative diseases of the central nervous system, such as general paralysis, tabes, etc. Chantemesse and Parlavecchio both studied the effect of nuclein injections on antibody formation, finding that both alexins and agglutinins were increased, while Fox and Lynch have in very recent years studied the effect of nuclein injections on the leukocytosis of dogs. Brown and Ross have studied the leukocytic

reaction in connection with injections in a series of mental diseases.

The dosage depends on the preparation. Usually as much as 0.5 gm. of the sodium nucleinate is given subcutaneously, this being followed by a leukocytosis in from 4 to 10 hours after the injection and a febrile reaction which may persist for 24 hours; this is usually mild in character and does not as a rule exceed 2° F.

A modification of this method is the *Nucleohexyl* recently prepared. It is a compound of nucleic acid and hexamethylintetramin that is used in 10% solution for intravenous injections. The dosage is about 10 c.c. Levy claims to have found it useful in the treatment of typhus fever.

### PROTEIN SPLIT PRODUCTS

That protein split products will, on injection, increase the tolerance both to further injections and resistance against infection is an observation that has been made quite a number of years ago, among others by Vaughan and his associates in this country. It is only in recent years, however, that the various split products of proteins have come to be recognized as therapeutic agents. Nolf has used proteoses in diseases associated with hemorrhage, as in hemorrhagic diathesis, paroxysmal hemoglobinuria, etc., with the idea of increasing the coagulability of the blood. To Lüdke belongs the credit of first using proteoses in the treatment of acute infections. Nolf began their use for this purpose somewhat later and since then a large number of clinicians have published their results with this distinctly "protein therapy" as it came to be termed.

In our experience a variety of *proteoses* (albumoses) prepared from different proteins, will give a very prompt and satisfactory reaction. It has been shown at various times that the primary proteoses are somewhat more toxic than the secondary proteoses for animals, but in therapeutic injections the difference in effect may not be appreciable. Lüdke used deuteroalbumoses, these being now prepared commercially for therapeutic use in Germany.

The derivation of the protein split product that is used is of considerable importance in regard to its toxicity. Schittenhelm and Weichardt in their studies noted the difference in toxicity of protein split products derived from different native proteins. Kaznelson studying this question with particular reference to the therapeutic use of deutero-albumoses tried out deutero-albumose prepared from fibrin, from gelatin, from wheat, horn, silk, etc. Injected subcutaneously they were all followed by considerable local pain at the site of the injection. Intragluteally the local reaction of these albumoses differed little from that following milk injection. The intravenous effect differed considerably. Thus the hetero-albumoses prepared from

fibrin were much more toxic than the others. Those from gelatin followed next in the severity of the reaction while those derived from wheat, horn, silk, etc., gave little or no reaction.

From the studies of Baehr and Pick it seems most probable that the toxicity of protein preparations such as these depends to a large degree on the presence or absence of the cyclic or ring compounds in the protein molecule. Perhaps, too, the size of the colloidal aggregate is of importance in determining the reaction after intravenous injection.

The dosage of the *Deutero-albumoses* and of the other primary and secondary proteoses so far used, has varied. In our own work we have used from  $\frac{1}{2}$  to 2 c.c. of a 2% solution of secondary proteose. Lüdke first used about 2 c.c. of a 2% solution; recently he has injected from 1 to 2 c.c. of a 10% solution; Holler used 1 c.c. of a 10% solution.

Jobling as well as the writer have been under the impression that small doses repeated at frequent intervals offer the best mode of administration. Jobling in his Harvey Lecture recommends beginning with a dose of 0.25 c.c. of a 1% solution and determining if the patient reacts with much temperature. If there is no general reaction from this dose a somewhat larger dose can be selected for injection the following day. This is particularly advisable in the more toxic forms of infectious diseases; in arthritis, on the other hand, it may be better to give a relatively large dose (after its reactivity is known) at the beginning and induce a sharp reaction. The reaction following the injection depends not only on the dose but on the type of disease from which the patient is suffering, just as with milk injections. (Schmidt.)

The patient does not become sensitized to proteose injections; rather a degree of tolerance is established, so that following or repeated injections do not give an equal response on the part of the patient.

In animal experimentation there is some evidence that sensitization, at least to the higher proteoses, can be established. In the human there has been no evidence of this effect, at least as far as can be determined from the clinical reaction that follows after repeated injections.

It is very doubtful to my mind if a therapeutic effect can be achieved unless a general reaction is brought about in the patient. Nolf emphasizes that shock should be avoided—"when one employs proteosotherapy to cure a patient of an infectious disease one should avoid shock—at least the violent shock which I have described. But it seems to be an advantage to produce a mild reaction which I have called the 'peptone effect' in contrast to 'peptone shock.'"

Efforts of many workers have been directed in producing some agent that would not produce a severe reaction—that is, the nausea,

chill, sweating and fever—and would at the same time give an equally satisfactory therapeutic result.

There is little doubt that from the clinical standpoints such an agent would be a very desirable one, and it is an idea that should be kept in mind. But we are confronted with the probability that, as will be pointed out in the chapter on The Focal Reaction, the positive phase or mechanism of recovery after nonspecific injections is a function, or at least very closely related to the degree of the negative phase or the intensification of the disease process that is clinically manifest in the reaction of the patient. Just as in local foci of disease a marked augmentation of the inflammation, both after specific vaccine injections (as after the injection of "Arthigon" Schultz found that gonorrheal lesions healed best after severe reactions) or nonspecific injections is followed as a rule by clinical improvement, so in the general infections a relatively severe reaction is more frequently followed by an abortive recovery than when the reaction is very mild or absent. I cannot too strongly emphasize, however, that the utmost care and judgment must be exercised and a considerable degree of experience must be gained in the treatment of such diseases as arthritis or of local inflammations before the attempt is made to treat general infections, unless the physician wishes to court disaster.

The entire question of dosage and of the proper reaction is still an open one. I believe that the method of Holler is a safe one and one that can be recommended. Holler injected his cases of infectious diseases with a daily dose of deuterio-albumose that was just sufficient to elicit a mild reaction. In some diseases he administered two doses daily. This method is certainly much safer than the administration of a single huge dose which may be more than the patient can bear.

v. Biedl has made use of *Histamin*, using 0.5 mg. for intravenous injections. The results were not particularly satisfactory, nor were they much better when *Witte Peptone* was employed.

On the other hand both Nolf and Gow have used *Witte Peptone* with evident success. Gow employs a 10% solution. This is made up by dissolving 10 gm. of the dry peptone in about 5 c.c. of hot freshly distilled water and bringing the volume up to 100 c.c. Of this from 8 to 10 c.c. are slowly injected intravenously.

The effect of the intravenous injection of various split products of proteins both from the physiological as well as the pharmacological standpoint has been intensively studied both in this country and in Europe and the literature is so well known and readily available that it will not be necessary to enter into it here. The effect of the intravenous injection of *Histamin* has been more recently studied by Dale and Laidlow.

They found that in cats the injection of from 1 to 2 mg. per kilo. was followed by a marked fall in blood pressure, there was a clumping of the blood platelets (for the significance of the clumping of blood platelets and its bearing on anaphylaxis the article of v. Behring is of interest), a leukopenia—the leukocytes stick to the lining of the vessels—and in a relative polycythemia with increased viscosity. These latter changes are due to the increased permeability of the capillaries, as a result of which they estimated that about 40 per cent. of the plasma was lost from the vascular bed.

### ENZYMES

**Trypsin.**—A method that was considerably exploited some years ago was the so-called Enzyme Treatment of cancer, advocated by Beard, which consisted in the subcutaneous injection of a trypsin solution. It is very problematical whether any malignant disease was ever actually cured by the injections; focal reactions were of course noted, with a diminution of the size of the larger tumors because of the increase in the autolytic processes in the neoplasm. The injection was practically always followed by a general reaction on the part of the patient, evidenced by the chill, sweating and temperature rise. After this acute reaction the patient would have several days of relative comfort. **Amylopsin** was usually combined with the trypsin for injection.

**Leukocytic Extracts.**—Leukocytes contain antibacterial substances (Moxter, Petterson, Schneider) and an effort was made to utilize this property therapeutically. Petterson used leukocytic extracts in dogs that were at the same time injected with anthrax bacilli; there was evidence of an increased resistance. Later he used a similar method in testing the increased resistance of guinea pigs treated with leukocytic extracts and infected with typhoid bacilli. Opie made similar experiments with dogs and later Hiss, and Hiss and Zinsser carried the method to actual trial in human infectious diseases. Leukocytes were as a rule obtained from rabbits, washed and suspended in distilled water. Usually the entire suspension was injected. Leukocytic extracts have been used in the treatment of pneumonia, staphylococcus infections, erysipelas, etc., with apparently favorable results.

Considering the enzyme content of the polymorphonuclear leukocyte it seems probable that the injection really represents a mixture of enzyme and heterologous protein, as far as the patient is concerned; the injection is followed by a leukocytosis (Alexander), but otherwise with little general constitutional reaction. Leukocytic extracts have been placed on the market for therapeutic use, and Archibald and Moore, Leonard and Harmer have published results obtained after the injection of leukocytic extracts. Tunnicliff, who has recently studied the effect of leukocyte injections, finds that the leukocytosis that is observed after the injection persists for from

1 to 4 days and that the leukocytes are particularly active (young forms).

#### TISSUE EXTRACTS

**Tumor Autolysates.**—Efforts to influence disease processes by means of autolysates from tissues and tissue extracts have centered largely about malignant neoplasms and a considerable number of substances have been used by clinical observers. The work of Beard has already been mentioned; the fact that tumor cells seem very rich in heterolytic proteoclastic enzyme (Wolff and Blumenthal) stimulated repeated efforts to prepare some substance from tumor juice that would have a therapeutic action. All substances so far used cause a typical protein reaction and are without specific action on tumor cells. The most recent report of such a preparation is that of Joannovics and his associate Scherber. Bier and Sticker began similar studies some twenty years ago, using foreign proteins (foreign serum, lymph, organ juices) combined with atoxyl.

**Cartilage Extracts.**—Heilner in recent years prepared an extract from cartilage called "sanarthrit" which, injected in chronic arthritis, causes in some cases marked alleviation of the symptoms. Heilner introduced the substance for the treatment of gout, on the assumption that in gouty diathesis the cartilage, because of its chemical structure, offered a site of particular affinity for the deposition of uric acid and related compounds. Therefore the injection of such material in a soluble form might aid in the elimination of the exciting metabolic products. It was soon found, however, that other arthritic processes, infectious in origin, were also influenced by the injections so that the theory was no longer tenable. It is now the expressed opinion of a number of observers that the reaction is merely a non-specific one and similar in character and in its therapeutic possibilities and limitations to the other agents of this group.

**Vascular Extracts.**—The most recent preparation of this nature is an extract of vascular tissue (blood vessel walls, etc.) which is said to have some effect in arteriosclerosis.

**Organotherapy.**—Borchardt, in recent communications, has made the statement that all the tissue extracts, unless they offer very definite glandular substitution, as thyroid extracts do, or contain enzymes (and are therefore enzymatic agents) represent merely nonspecific agents which stimulate the organism in a nonspecific way. It is at least very probable that in a measure their effect is due to such activity.

Borchardt is also of the opinion that the injection of relatively small amounts of blood subcutaneously (Weinland) and the injection of marrow extracts (Danilewski, Fowler, etc.) as well as splenic extracts have their therapeutic basis on the same nonspecific stimulation of the hematopoietic system.

Esch considers the results obtained with organotherapy in menstrual disturbances from the same point of view. As proof of the plasmaactivation Borchardt brings a number of interesting experiments. Using immunized rabbits he has found that the injection of asthmolysin (0.0008 adrenalin and 0.04 infundibular extract), of spermin and also of thyroid extract greatly increased the titer of the immune bodies in the serum. The thyroid extract was active even when given by mouth. As a result of his experiments he considers any of these agents useful in the infectious diseases.

### THE VACCINES

Before taking up the question of the use of vaccines in producing a nonspecific response it may be well to quote briefly from a recent paper of Wright. Inasmuch as Wright has done more than any other immunologist to emphasize the factor of strict specificity in vaccine therapy, introduced the method of estimating such specific response on the part of the patient by means of the opsonic index, recommended the use of autogenous vaccines, etc., it is but fitting to record his present attitude.

“Let me start quite at the beginning. Long after the principle of prophylactic inoculation had established itself in medicine, it was accepted that to inoculate microbes into the already infected system would be as illogical as to instill further poison into an already poisoned system. Pasteur was the first to teach us here a distinction. He pointed out, in connection with immunization against rabies, that a vaccine might legitimately come into application in the incubation period. That was the beginning of therapeutic immunization; and from that time forth it was recognized that you may legitimately inoculate in the incubation stage, and try to get in advance of the infection. But it was in everybody's mind that immunization took 10 days to establish itself. When I showed in connection with antityphoid inoculation that bactericidal substances were very rapidly elaborated, it became plain that this involved shifting the old landmarks and taking in further territory for therapeutic immunization, and one had to ask oneself all sorts of penetrating questions. One had to ask oneself in connection with ‘generalized infections’ at what particular stage of the infection one was to regard the body as overmastered by the bacterial poison, and incapable of further immunizing response. Again, in connection with ‘localized infections’ one had to inquire whether they should not be envisaged as general infections indefinitely arrested in their incubation stage, and whether they might not, in consonance with that, be brought within the sphere of inoculation.

“Further consideration suggested that the problem of therapeutic inoculation can be approached also from a point of view different from that taken up by Pasteur. With respect to immunizing response, the body had been visualized as a single and undivided unit. That is clearly erroneous. One region of the body may be making immunizing response while the other is inactive. For instance, in the stage of incubation it is presumably

only the region which is actually harboring the microbe, and in the stage of generalized infection it is presumably the entire body which is incited to respond. And again, in localized infection we may—making here some reserves—assume that we have only localized response.

“Placing ourselves at this point of outlook, therapeutic immunization will, it is clear, be theoretically admissible so long as there remains in the body any part which is not already making its maximum immunizing response. And the program of therapeutic inoculation would accordingly consist in exploiting in the interest of the infected regions of the body the immunizing responses of the regions which are uninfected.

*“Results of Vaccine Therapy*

“Keeping that now in view, let me try, very briefly, to tell you what are, in my view, the results which have been achieved by applying this therapeutic method. I can do that in a very few words.

“In every form of infection a certain quota of unequivocal successes may be credited to the method, and especially successful results have been obtained in furunculosis and acute inflammatory sycosis; in ‘poisoned wounds’—meaning by that localized cellulitis set up by a streptococcus infection; in streptococcal infections taking the form of lymphangitis, in erysipelas; in tubercular adenitis, tubercular joint infections, tubercular dactylitis, tubercular orchitis, and tuberculous infections of the eye, especially in phlyctenules of the conjunctiva; again in bronchitis, in cholecystitis, and gonorrheal rheumatism. The most dramatic and convincing—convincing because here no other therapeutic measures are employed as adjuncts—are the successes obtained in streptococcal lymphangitis, in streptococcal cellulitis—I am thinking of those cases which have already been incised without striking benefit—and in conjunctival phlyctenules.

“When we analyze the successes and failures\* of vaccine therapy the following points come out quite clearly:—

“(1) Vaccine therapy is generally unsuccessful where the infection—as in phthisis—is producing constitutional disturbance and recurring pyrexia.

“(2) Vaccine therapy is also generally unsuccessful where we have to deal with unopened abscesses, or sloughing wounds with corrupt discharges.

“(3) In long-standing infections vaccine therapy is much less successful than in recent infections.

“To see what auxiliary measures should be applied in these cases, I must take you back for a moment to the region of general principles. . . .

\*I here, as clear thinking exacts, exclude from the failures of vaccine therapy the failures of that preventive inoculation against individual infections to which vaccine therapy is the usual precursor. The efficacy of such prophylactic procedure is a question apart. But I may usefully point out to you that the superior credit which attaches to antityphoid inoculation, and preventive inoculation against infective diseases generally, as compared with preventive inoculation against what I may call individual infections, is probably attributable to the fact that, in the case where we are dealing with an infective disease, the external circumstances are as favorable to success as they are in the case of inoculation against “individual infections” unfavorable.

*"Nonspecific Immunization"*

"In the foreground stands the question of nonspecific immunization. That immunization is always strictly specific counts as an article of faith; and it passes as axiomatic that microbic infections can be warded off only by working with homologous vaccines; and that we must in every case before employing a vaccine therapeutically, make sure that the patient is harboring the corresponding microbes. I confess to having shared the conviction that immunization is always strictly specific. Twenty years ago, when it was alleged, before the Indian Plague Commission, that anti-plague inoculation had cured eczema, gonorrhoea, and other miscellaneous infections, I thought the matter undeserving of examination. I took the same view when it was reported in connection with antityphoid inoculation that it rendered the patients much less susceptible to malaria. Again, seven years ago, when applying pneumococcus inoculations as a preventive against pneumonia in the Transvaal mines, I nourished exactly the same prejudices. But here the statistical results which were obtained in the Premier Mine demonstrated that the pneumococcus inoculations had, in addition to bringing down the mortality from pneumonia by 85 per cent, reduced also the mortality from 'other diseases' by 50 per cent. From that on we had to take up into our categories the fact that inoculation produces in addition to 'direct' also 'collateral' immunization. This once recognized, presumptive evidence of collateral immunization began gradually to filter into our minds. Among, I suppose, many thousands of patients treated by vaccine therapy in private and in hospital, it happened every now and then that a patient was treated with a vaccine which did not correspond with his infection, and that that patient indubitably benefited. Again, it was not an uncommon experience for the subjects of a very chronic infection (such as pyorrhoea) who were treated first by a stock vaccine, and afterwards with an auto-vaccine, to assert that they derived more benefit from, and to ask to be put back upon treatment by the stock vaccine.

"From such cases hints are conveyed to us that there may exist a useful sphere of application for collateral immunization; and that such sphere may, perhaps, be found in those cases where the infection is of very long standing, and where the patient has become very sensitive to, and has probably come very near the end of his tether in the matter of immunizing response to, the particular species or strain of microbe with which he is infected. It will, with regard to such patients, be remembered that they constitute the third of those three classes of cases to which I referred to at the outset of this lecture as very intractable to vaccine therapy.

"We are, however, here considering primarily the question of principle; and in connection with this what is of fundamental importance is: that we should discard the confident dogmatic belief that immunization must be strictly specific, and that we should in every case of failure endeavor to make our immunization more and more strictly specific. We should instead proceed upon the principle that the best vaccine to employ will always be the vaccine which gives on trial the best immunizing response against the microbe we propose to combat.

"I would point out that this would almost certainly not involve any revolutionary change in the accepted practice in either serum therapy or

in prophylactic or ordinary therapeutic inoculation. But it would mean taking into account in cases which proved intractable to treatment with the homologous vaccine the possibility of seeking for collateral immunization by inoculating a microbe or mixture of microbes other than that with which the patient is infected. The trial of this procedure might perhaps recommend itself where from the outset there is very little immunizing response to the homologous vaccine, and also where, as in long-standing cases of tubercle or streptococcus infection, the power of direct immunizing response to the corresponding vaccines is becoming exhausted."

This use of bacterial vaccines for "collateral immunization" as Wright uses the term, or for nonspecific stimulation, is a modern conception that dates practically from the work of Renaud and of Kraus. The former used typhoid vaccine in the treatment of a number of non-typhoidal diseases; the latter treated typhoid patients with colon vaccine, and then proceeded to treat puerperal infection and other acute infections with typhoid and colon vaccines with remarkable results. Until this time the fear of overdosage had kept back investigation in this particular field. The disastrous effects that had at times followed the injection of tuberculin in tuberculosis had made a profound impression on medical men, and the emphasis placed on the negative phase of the opsonic curve after vaccine injection had a similar effect. With the introduction of the sensitized vaccines of the French school larger doses came to be used, but here again a generalized reaction was avoided. Occasionally one finds records of more heroic dosage and cures following on general reactions; thus Szily cured a severe ophthalmoblennorrhoea with several large doses of gonococcus vaccine.

Following the publication of Kraus's results a large number of observers have used heterovaccinotherapy in the treatment of diseases of various kinds. The reaction of these various bacterial vaccines varies of course; in general, however, the following bacteria have given results.

**Typhoid Vaccine.**—The toxicity varies greatly with the age and the strain. For convenience the vaccine is usually made up with 100 million organisms to the cubic centimeter, of this approximately 25 to 50 million may be given at the first dose if the particular vaccine is not too toxic; great care must be observed. Typhoid vaccine is followed by a prompt chill and temperature reaction, usually by a leukocytosis. Headache is a common accompaniment.

**Colon Vaccine.**—Colon vaccine is usually followed by a severe reaction, which may, however, be delayed for several hours after the injection. Headache is usually severe after several hours. It has been used more frequently by English observers. The dosage should not exceed 25 million for the first intravenous injection; for later reactions this may be increased.

**Dysentery.**—Dysentery strains of all types when injected, both

subcutaneously or intravenously, are relatively toxic and resemble typhoid and colon vaccines in their general effects.

**Cholera, prodigiosus, proteus,** and a number of other organisms have been injected intravenously by various observers.

**Meningococci.**—The dose used is usually about 100 million. The injection is followed by a prompt chill that has its onset in from 15 minutes to one hour and lasts usually a half hour. Headache is common, nausea and vomiting quite exceptional. The temperature rise is marked and reaches its maximum in from 6 to 8 hours. Herpes has been commonly observed after the injections.

**Gonococci.**—Dosage and reaction similar to the meningococcus. Leukocytosis is well marked with both types of organisms and reaches a maximum in from 5 to 7 hours. With the gonococcus vaccine herpes is less frequent.

**Streptococci.**—The streptococcus is evidently not as toxic as the typhoid and colon bacilli, and the reaction is frequently delayed from 8 to 10 hours. A dosage of 100 million is usually followed by only a mild temperature reaction. A chill is not so common and the leukocytosis is lacking. The vaccine does not seem to be a good agent for nonspecific stimulation.

**Staphylococci.**—Similar in dosage and in reactivity to the streptococcus vaccine. Followed by a leukocytosis of considerable extent and has been found more useful than the streptococcus vaccine.

**Pyocyaneus.**—Pyocyaneus Vaccine was one of the first used for heterovaccinotherapy (by Rumpf in the treatment of typhoid in 1893). Its use has not been extensive enough to justify any conclusions as to its value. Döllken has used it in the treatment of gummata.

**Pneumococcus.**—In dosage and reaction similar to the streptococcus, with a certain degree of latitude with different strains. The leukocytic response is not marked; indeed may at times be absent.

**Influenza Bacilli.**—Influenza bacilli injected intravenously have been given in doses of from 50 to 100 million organisms with relatively little reaction on the part of the patient. There is as a rule no chill, but the temperature response may be from 2° to 3° F. several hours after the injection.

**Diphtheroids.**—Both diphtheroids and diphtheria bacilli seem to produce little reaction when injected intravenously. A dosage of from 25 to 200 has been injected intravenously, followed after a long latent period (10 hours) by some general reaction, slight chill, temperature rise of from 1° to 2° F. and headache. Usually there is no leukocytosis.

While all these organisms may produce some reaction, either mild or severe, they are by no means quite comparable in their effect on the leukocytic response. Schittenhelm, Weichardt and Greisshammer have called attention to some of the differences that exist follow-

ing the intravenous injection of different kinds of bacteria, certain organisms being followed by a prolonged leukopenia instead of a leukocytosis, others producing myelitic stimulation, others a lymphatic stimulation, etc. Döllken in his recent discussion and study of heterobacteriotherapy brings out the fact that the stimulation by different bacteria may not be omniscellular, but rather selective; that the clinical result, too, is by no means independent of the kind of organism injected. Thus he found that while pyocyaneus vaccine was effective in gummata, a pseudodiphtheria vaccine was quite without effect. In neuralgia a prodigious vaccine gave an excellent clinical result, while cholera and dysentery vaccine was not followed by equal clinical improvement. In a like measure in the treatment of acne neither prodigious nor pyocyaneus vaccine proved useful, while the autogenous vaccine was promptly followed by improvement.

The injection of vaccines is not, like milk, followed by any styptic effect; on the other hand, they are not as a rule hemolytic, as nucleohistone and albumoses may be. The resistance to reinjection also differs with the different organisms. Thus there is a rapid tolerance, or increased resistance established to typhoid, pyocyaneus, pseudodiphtheria and several other vaccines, while milk, representing a native protein, may at times become more marked in its effect with subsequent injections.

**Mixtures of vaccines** have also been employed. Thus the "Arthigon" of Bruck contained a number of strains of gonococci and 10% of protargol and was used extensively in Germany in the treatment of gonorrhoeal complications. "Vaccinurin" is a recent mixture recommended by Döllken for use in neuralgia and neuritis and consists of prodigious organisms and staphylococci which have been permitted to autolyze.

*Danysz' method* of treating disease has been discussed in full in a recent number of the *Bulletin médicale*. He describes anew the technic and his experience in 352 cases since 1913. In seeking for an efficient antianaphylactic, he started from the theory that the focus of production of the substances generating the anaphylaxis in the majority, if not in all, of the chronic, noncontagious diseases, is in the bowel: The albuminoid matters or microbial contents of the intestinal canal passing into the blood through the congested intestinal mucosa act as antigens and induce the anaphylactic state of the organism. Consequently, he reasoned, the microbes isolated from the intestinal contents ought to act as antigens when inoculated or ingested. The microbes are isolated from a scrap of stool by sowing on ordinary culture bouillon and then making pure cultures on gelose, and then mixing the cultures in the same proportions as found originally. This is diluted with physiologic serum, sterilized with heat and the dose determined by weight. For ingestion, the dose is 1/10 to 5/10 mg. of the microbial bodies; for injection 1/1,000 or 1/1,200 mg. At first he made an autogenous antigen for each patient, but finding that the species and

proportions of bacteria were so uniform, he used a polyvalent heterogeneous preparation in some cases.

*Much's Antigen.*—Much has recently described a vaccine which he terms "Immunvollvaccine" for intramuscular injection, which he has used in the treatment of influenza. It is prepared from a number of nonspecific antigens: (a) Reactive proteins, the metabolic products of several nonpathogenic bacteria, (b) a lipoid mixture from bile, and (c) a fat mixture of animal derivation. The theory underlying such a mixture is that of partial antigens which he has developed in tuberculosis.

#### BACTERIAL EXTRACTS AND RELATED SUBSTANCES

The use of bacterial extracts and of bacterial growth products to produce a nonspecific temperature increase is not a recent innovation.

**Tuberculins** have been used for this purpose for some time, especially in the treatment of paresis, as introduced by v. Jauregg. For this purpose a relatively large dose is used, beginning with 0.01 mg. and increasing rapidly until as much as 0.5 mg. is injected. The temperature reaction is a prolonged one; usually a leukocytosis is produced. It offers no particular advantages over milk injections which produce practically the same results.

Kaiser has used **Tebelon**, the isobutyl ester of oleic acid (introduced by Stoeltzner), in a number of surgical conditions. Like other nonspecific substances it acts as a pyrogenic agent even in nontuberculous diseases.

**Typhin.**—Biedl in 1915 noted that the nonspecific reaction could be elicited with histamin, the toxicity of which had been previously studied. v. Groer made use of this knowledge in preparing a mixture of nucleoprotein and histamin from typhoid bacilli which he called "typhin" to be used in place of whole bacilli for intravenous injections. The chief advantage of the preparation lay in the fact that with such a substance the dosage might be standardized and the reaction gauged. With this "typhin" v. Groer treated 23 cases of typhoid, of whom 18 made a prompt recovery and 5 died. In the case of a typhoid patient that recovered by crisis after the injection and died a few days later from an intercurrent condition, v. Groer observed at the autopsy that the ulceration of the bowel had practically healed and that the spleen was small (v. Wiesner has recorded similar observations).

It is interesting to note that v. Groer found no increase of antibodies in the serum of patients after the injection despite the fact that such patients made an excellent and prompt recovery after the injections.

Intramuscular injections are recommended for common use. He also gave small doses of digitalis a few days preceding the injection in severely toxic cases.

**Coley's Fluid.**—This consists of fluid culture products of the streptococcus and pyocyanus. It is used particularly in sarcomata in which it was usually followed by a severe systemic reaction and some evidence of digestion and autolysis of the tumor, but never to the extent of complete eradication of the neoplasm.

**Pneumococcus Autolysate.**—Among bacterial autolysates which were prepared on a specific basis but which in all probability were effective, when therapeutically active, as nonspecific agents were the pneumococcus autolysates of Rosenow, recommended for use in lobar pneumonia.

**Phylacogens** (*Schafer's Vaccine.*)—These represented bacterial growth products of a number of bacteria first prepared by Schafer and used with some success in arthritis. They were later prepared on a commercial scale and marketed under the trade name of Phylacogens. Inasmuch as the method of preparation and exact composition is not known, the reaction merely a nonspecific one, other and less expensive agents will be found more satisfactory and more easily controlled.

#### COLLOIDAL METALS

Colloidal metals were perhaps first used as therapeutic agents by Credé in 1895. Credé used silver preparations on the assumption that they were actively streptococcidal, and they were introduced by him in the treatment of streptococcus infections. The range of application was, however, soon extended to septic conditions in general (it was no longer considered a specific streptococcicide but to possess heterobactericidal properties) and latterly it has been surmised that its usefulness depended not on its particular chemical structure but on properties of colloidal metals in general which produced the nonspecific reaction and were therefore typical ergotropic agents. Earlier workers had followed Credé in the interpretation of the method of action (Marquis dos Santos and Alphonse Pinto); Albrecht surmised that the catalytic property of the finely dispersed metals might have a definite relation to the therapeutic effect; while later the reactive leukocytosis that followed the injections was studied and held responsible for the therapeutic result. (Dunger, Sahli, Bruntz and Spillmann.)

Bonnaire and Kausch both noted and emphasized the important fact that following the intravenous injection a chill, fever and leukocytosis were commonly observed. This febrile reaction, just as in other nonspecific reactions, varies considerably with the disease process. In sepsis Kausch noted that the high temperature dropped promptly by lysis, whereas afebrile cases, such as carcinoma, responded

with a sharp febrile rise. Eberstadt in treating erysipelas did not observe any initial rise in temperature following the injection; a lysis occurred in his four cases.

The fact that colloidal metals are active catalytic agents has led to the theory that in the organism they act therapeutically by virtue of this property as inorganic ferments. Vergely in a recent review calls attention to this effect in connection with the enormous surface developed by colloidal preparations of this type. A liter of a 0.5 per thousand solution of colloidal gold, for example, presents a surface of 150,000 square centimeters, while the same weight of gold in a compact form presents a surface of only 50 square millimeters. In therapeutics, they whip up the organism but if it is unable to respond, they can do no good. If the patient is unable to produce more leukocytes, there is no chance of success. In selecting the colloid to use, he advises the metal that has been found most active against the bacteria, etc., involved. He adds that injection of a colloid may favor the production of a fixation abscess when this is attempted at the same time. There is a place for colloidal therapeutics, he concludes, besides vaccine therapy and serotherapy, but its principal indication is in chronic disease or infection.

While the reaction that follows the injection of colloidal metals may be quite severe, relatively few untoward effects have so far been reported in the medical press. Eyth and Moser have reported deaths; Saito, Eberstadt, Kausch and Werler have reported severe shock reactions. Injections must be made very slowly; therapeutic results can be expected only when the metals are given early in the disease process.

A variety of colloidal metals have been prepared for therapeutic use, some of which are on the market as commercial preparations. The colloidal silver-albumen preparations have been used longest. Arsenic, iodine, manganese-copper and platinum, zinc, manganese, gold, iron, sulphur, mercury, tin oxide, etc., have been used with varying success. The dosage depends of course on the amount of metal dispersed in the solution and on the degree of reaction produced, both variable factors, that require a certain amount of trial for each preparation. The treatise of Searle covers the field of recent English work with colloidal metals.

Of the silver preparation the dosage has varied in practice from the minute doses given by Gellhaus, who used fractions of a cubic centimeter, to those of Kausch, who commonly injected from 10 to 25 c.c. and even gave as much as 100 c.c. of a 2% solution intravenously.

The colloidal metals are given not only intravenously and subcutaneously, but have been used locally, given per os and even as clysmas. Alexander, for instance, gives first one injection intravenously (10 c.c. of a 2% solution), then follows the next day with a

clyisma of 50 c.c. of a 5% solution. K. and R. Klotz have used it in the form of a clyisma, giving 1 mg. daily during the course of pneumonia.

The question arises in connection with the injection of these metallic preparations how much of the reaction, and consequently of the therapeutic benefit, is due to the dispersed metal and how much to the protective colloid that the manufacturer adds to his solution to make it stable. Thus for the commercial iodo-collargol preparation the composition is stated by the manufacturer to be 31% in silver, 37% iodine and 31% protective colloid. Other preparations vary in the amount of protective colloid added and the substances used for this purpose.

Auld has published some illuminating experiences in this connection. He had been working with colloidal platinum solutions for several years and found one particular preparation very effective therapeutically. This was an old solution that had been in his laboratory for some time. Intravenous injections of from 3 to 7 c.c. resulted invariably in a sharp reaction on the part of the patient—a chill commencing in about half an hour, the temperature rising to 104° F. and 105° F. and the patient complaining of nausea and headache. This reaction occurred both in normal individuals and in patients suffering from a variety of ailments. His other platinum preparations did not give this sharp reaction and the therapeutic effect likewise was lacking. On further investigation of the matter Auld ascertained from the manufacturers that this particular preparation had been stabilized by a solution of veal peptone (0.4%) together with 1% glucose. This peptone on trial gave an identical reaction on the part of the patient as the original platinum solution and could be used therapeutically with equal success.

The use of the colloidal metals has been very extensive in a variety of clinical fields, both for septic conditions as well as in certain special conditions such as skin diseases, venereal diseases, etc. Thus Reichmann has obtained good results in sepsis, endocarditis and rheumatism; Bichon in rheumatic iritis; Salomon, and Labbe and Moussaud (colloidal gold) in typhoid; Richter in trench fever; Klewitz in endocarditis. A number of general articles covering the subject have been published which will be found of interest: Guaita, Meyer, Kausch, Bockemueller, Cowadias, Loeper and Wahram, Laumonier, etc.

It has been found that after the injection the colloidal metal is deposited chiefly in the liver, the spleen and the bone marrow (Voight). A separate field for therapeutic application of the colloidal metals lies in their use as adjuvant agents in radiotherapy. In this connection considerable progress has been made in recent years.

The colloidal metals, like many of the other nonspecific agents, are as a rule less active on reinjection. Böttner, however, believes that he has been able to demonstrate that the organism may be sensitized to collargol and that on reinjection in proper time intervals, the patient will react more strongly than with the first injection.

This has a definite value in such conditions as arthritis where a sharp reaction on the part of the patient is usually very desirable.

#### MISCELLANEOUS

**Hypertonic and Hypotonic Salt Solutions.**—The injection of large intravenous doses of salt solution in the treatment of typhoid fever dates from the report of Engländer. Engländer while treating a case of typhoid that had had a severe hemorrhage injected some 300 c.c. of normal saline intravenously. This was followed shortly after the injection by a severe chill, and the usual nonspecific reaction. The following day the temperature declined to 35.2° C. (95.4° F.), and the patient made a prompt recovery by lysis that commenced the day following the injection. Other cases were then treated by Engländer with the same method.

Sodium chlorid cannot, however, in the light of our present knowledge be considered as an indifferent substance to the organism. The observation of Hutinel that salt causes fever even when injected in infants in small doses has been the subject of considerable discussion, Samelson contending that such temperature disturbance was due to the fact that impurities were injected with the salt or in the water used in making up the salt solution. Bendix and Bergmann came to the same conclusion. More recent observations concerning the rôle of the sodium ion in its relation to the permeability of cell membranes, and the rôle of the water content of the tissues in the mechanism of fever leave the status somewhat uncertain.

Instead of using large doses and producing a marked reaction in the patient as Engländer did, Daniélopolu has used repeated small doses of hypotonic salt solution (.065) in the treatment of typhus fever. By this method he claims to have obtained remarkable results.

Two other methods have been devised in which salt solutions are used, both for local injection. Eisel has injected from 10 to 15 c.c. of physiological salt solution locally between the scrotum and tunica vaginalis in cases of epididymitis. It is said to be followed by a diminution of pain and hastening of resorption.

The production of salt abscesses is another method recently devised, but one that cannot be recommended. This is produced by injecting a (5 to 8 c.c.) concentrated solution of salt intramuscularly (30 parts sodium chlorid, 1 part calcium chlorid, 100 parts water) and was recommended by v. Szily and Stransky. Needless to state, in this case an abscess usually forms and from it autolytic products are absorbed; as Luithlin has pointed out, it is merely a form of the older "fixation abscess" of Fochier with the disadvantage that the method is very painful and leads frequently to complications. Raege and Zieler, who have both used the method, condemn it.

**Sugar Solutions.**—The use of sugar solutions (usually glucose) for intravenous injections in sepsis, in pneumonia and other infectious diseases has been repeatedly reported, with some evidence of clinical usefulness. There is usually a slight temperature reaction following the injection and a leukocytosis of from 5,000 to 20,000. Audain and Masmonteil inject from 500 to 2,000 c.c. daily and report satisfactory results in sepsis, erysipelas and rheumatism. The isotonic solutions are made up as follows: For glucose 47.6 p.m., for saccharose 103.5 p.m., for lactose 108.9 p.m.

The use of sugar injections in the treatment of tuberculosis led Hasenbein to suggest sugar injections to produce focal reactions in general. He used a 50% solution of cane sugar in doses of from 3 to 5 c.c. to which was added 1 c.c. of a 2% solution of novocain (intramuscular injection). In females suffering from gonorrhoea there was a typical focal reaction with first an increased secretion, followed later by a diminution.

**Distilled Water.**—Reactions have been reported from distilled water when injected in relatively large amounts intravenously.

**Formalin.**—Torry, working with acute and chronic rheumatism, has injected formaldehyd intravenously to produce the shock reaction. The toxic agent which brings about the reaction according to Torry is probably a formaldehyd-protein compound. The dosage is as follows: Formalin is used (37% solution of formaldehyd) and of this from 1.5 to 3 c.c. are injected after diluting in from 200 to 300 c.c. of physiological salt solution.

During the administration there is some bronchial irritation and lacrimation. After the injection a typical protein shock reaction occurs in about half an hour's time, i.e., chill, fever, sweating, etc.

**Solusin.**—From Szily's laboratory another chemical mixture has been published, interesting rather than useful. This consists of 1.4 parts of bichlorid of mercury, 0.5 part sodium arsenate, 24 parts of sodium iodid and distilled water 100 parts. Of this mixture from 1 to 2 c.c. are injected and the patient is said to react with a typical chill, fever, sweating, etc. *Ammoniacal copper sulphate* in a 4% solution has been used by Noire for intravenous injection in puerperal infections.

**Hetol**, the sodium salt of cinnamic acid, **Sodium Succinate**, **Succinimid**, **Levurine** and **Tylmarin**, **Formic Acid** (Krull), to mention but a few of the drugs that have been used as nonspecific stimulants, are all characterized by a leukocytosis following their injection.

The use of the active toxic agent of *Bee stings* and *Snake Venom* has been reported for a number of diseases, the former with particular success by Terc and Langer in the treatment of arthritis.

**Iodids.**—A discussion of the probable mechanism of the therapeutic effect of the iodids might be of value in this connection, but inasmuch as

the subject should be treated together with a number of related chemical problems in an extended manner, the present treatise will not offer a suitable opportunity. Jobling and Petersen have discussed some of the features in a paper published in the *Archives of Internal Medicine*, where the literature will be found. It seems very probable that the iodids play a considerable rôle in the stimulation of tissue, particularly in the enzyme phenomena. Sherrick's and Sollmann's interesting observations on the alteration of the reactivity of the skin to cutaneous injections, the reaction of tuberculous patients (Petersen) and of carcinoma patients (Moresowa) are but a few instances of this effect. The property of the iodids in increasing the rate of diffusion of a number of substances in colloidal systems evidently is closely related to their therapeutic effect.

**Turpentine.**—The use of turpentine for subcutaneous injections is an old procedure that in a modified form has been very recently reintroduced in the treatment of skin diseases and inflammatory conditions. Fochier in the early nineties had introduced the "Fixation Abscess" as it was termed, produced by injecting about 1 c.c. of turpentine subcutaneously and intramuscularly. The abscess was used in certain acute infections, including pneumonia, puerperal fevers, adnexal inflammation, etc. In many ways this was merely the reintroduction of the very ancient method of producing an "issue" by the use of seton or fontanelle.

More recently the French and German clinicians have modified this method and are now injecting minute quantities of turpentine (20% of turpentine in olive oil) intramuscularly in frequently repeated doses. The mechanism involved is merely the production of a multitude of small sterile areas of inflammation and necrosis, with tissue stimulation from these foci. It is said to be used with success in a number of skin diseases and the French observers have used it extensively in the treatment of influenzal pneumonia, etc.

According to Karo the turpentine mixture in olive oil—4 parts in 16 parts of olive oil—is borne much better if one adds a sedative such as eukupine. This lessens the pain at the site of injection. Naturally care must be taken to avoid the subcutaneous tissues and inject wholly intramuscularly.

Karo has more recently recommended the use of "Terpichin." This is absolutely free from rosins and oxids and is combined with quinin which seems to increase its activity. The injections which are similar to those of turpentine—intragluteal and usually biweekly—are followed by a well marked general stimulation of the patient as well as a leukocytosis.

**Antipyretics.**—The nonspecific effect—plasmaactivation—that results from the use of certain drugs has recently been studied by Königer. He has come to the conclusion that the antipyretics have such an effect quite apart from the usual pharmacological effect heretofore studied, an effect which can be demonstrated if the dosage

is given in proper intervals. The effect is diphasic, as with all other nonspecific agents.

**Yeast.**—The use of yeast is an ancient one in therapy. Hippocrates is supposed to have applied it in the treatment of leukorrhea; during the Middle Ages it is said to have been prescribed in plague; it was not until the middle of the last century, however, that it was used on a larger scale (Mosse) and since then its popularity has gone through several cycles of advance and of decline. In furunculosis, in anthrax, in diabetes, in suppurative processes, in diseases of the gastro-intestinal tract, in arthritis, and in sepsis it found many adherents during the earlier revival but by the end of the century it had again practically vanished as a therapeutic measure. Brocq revived its use in 1899. In the period from 1900 to 1907 a great number of clinical reports were published, together with some experimental data (Lardier, Krause, Hedrich); more recently Hawk and his associates have published a series of cases, chiefly acne, (*vulgaris* and *rosacea*) and furunculosis, in which excellent results were obtained by yeast therapy. Besides the skin diseases, Hawk and his coworkers reported favorable results in acute bronchitis, urethritis, conjunctivitis, arthritis deformans, etc. In all of these conditions it is reported that, apart from any influence on the local pathological condition, the general nutrition of the patient was improved. Even when given via the intestinal tract there is evidence of a stimulating effect of the yeast in the leukocytosis which is demonstrable after its use.

Recently Wolf and Lewis have endeavored to establish some basis for the therapeutic use of yeast by investigating whether the ingestion of yeast would in any way influence the antibody titer of the serum of experimental animals. Their results were negative.

**Light Rays—Roentgen Rays—Radium—Photodynamic Agents.**—These agents may in some measure bring about a systematic reaction on the part of the patient, depending on the dosage, the organ or the pathological tissue irradiated and the amount of necrosis already present or produced by the agents under consideration. All these agents first stimulate tissue cells, later with prolonged exposure, cause the death of the cell. In both cases substances enter the blood stream that cause a general reaction on the part of the patient; this may be mild in character, may cause a severe febrile reaction, or even complete shock with lowered blood pressure, prostration, and even death. After the moderate reactions of this type, if the patient is in fairly good condition and able to respond, a definite euphoria, an improvement of the appetite, nutrition and general well-being may set in, just as after other nonspecific agents.

In this category must be placed the effect of heliotherapy in the treatment of tuberculosis and other chronic infections, the effect of

remote Roentgen irradiation on asthma (Schilling-Drey and Losser, etc.), on the hastening of ossification (Stettner), on furunculosis (Schrews), on local inflammatory processes (Kaznelson and St. Lorent), the effect of radium on arthritis, gout, adnexal inflammation, etc. (Gudzent).

The shock following actual *burns* or that following the effect of *photodynamic* agents such as those introduced and studied by von Tappeiner, has its place in this same category. (Pfeiffer.)

**Biological Alterations.**—As will be pointed out more fully in the chapter on The Focal Reaction, it is very probable that a variety of alterations in the organism may bring about effects on pathological processes similar to those that we induce artificially with nonspecific injections. The menstrual cycle and pregnancy, chilling, prolonged exercise, intoxication arising from faulty gastrointestinal absorption, starvation, even endocrine disturbance and the effect of nervous excitation must be considered from this point of view.

In a like manner the products of an inflammatory reaction in one tissue may bring about a nonspecific reaction of the entire organism and so alter pathological processes elsewhere. A number of dermatologists have called attention to this possibility in connection with the clinical observation that in extensive luetic or tuberculous lesions of the skin the internal organs are apt to be relatively free from disease. The discussion of these problems will be taken up in a later chapter.

**Depression Immunity.**—Even acute diseases are profoundly altered by shock effects due to intercurrent conditions. Thus the malarial paroxysm will in the typhoid patient frequently bring about either a temporary or permanent detoxication (Zupnik, v. Müller and Leiner), and v. Jauregg has even inoculated patients with malarial plasmodia (in cases of paresis) as a therapeutic measure. The acceleration of wound healing after erysipelas (Goebel), or the effect of erysipelas on tumor growth, the effect of pregnancy on tumor growth (Slye) are all related phenomena. Morgenroth, Biberstein and Schnitzer have recently studied immunity conditions bearing on this problem which can only briefly be outlined at this time. They have been experimenting with superinfection or superimposed infection, as this field of investigation has thus far resisted any attempts to harmonize its findings with the prevailing theories in regard to immunity, and as experimental studies in this field seemed to promise good results. They started with the commonly accepted theory that the infected organism acquires an immunity against superinfection, and against a like, superimposed infection, but they became interested in the investigations of Landsteiner and Finger, who maintain that the organism infected with syphilis is by no means immune to a new syphilitic infection, as has been commonly supposed. Their experiments demonstrated that mice with an experimental, chronic streptococcus infection, streptococci being found in the blood and in the organs, possess immunity toward a superinfection with

streptococci, as is shown by the fact that when given a streptococcus dose, such as will kill normal animals within twenty-four hours, they show no change in their behavior. They are immune not only toward the strain of streptococcus with which they were primarily infected but also against foreign strains of streptococcus. However, this immunity is not absolute but relative, for it is broken down by a strain of especially high virulence, in which case the infection runs an acutely fatal course, as in the controls. This partial immunity does not lie in the fact that the superinfection does not "take"; on the contrary, the streptococci used for the superinfection appear in the blood and organs, and by the aid of especially "marked" strains could be shown to remain present for some time. The partial immunity consists, therefore, merely in a depression of the virulence of the infection. This immunity was developed in from six to twenty-four hours after the experimental infection. It does not seem to have anything to do with anaphylaxis, but presents a new kind of immunity. They theorize that the passing of an acute infection into a chronic phase is conditioned by the development of this "depression immunity." The latter is not the result of the chronic infection, but every infection that is not rapidly fatal has its course determined by the depression immunity. Each phase of the infection is the result of the antagonism between the causal germ and the degree of depression immunity at the moment. This assumption throws light on natural immunity and all other forms of immunity which do not fit into the picture of immunity from antibody production.

Otto Wiegand has recently contributed to the same subject and Berliner and Citron working with chicken cholera in guinea-pigs have confirmed the findings of Morgenroth and his associates.

## CHAPTER III

### THE NONSPECIFIC REACTION

The intravenous injection of bacterial suspensions such as typhoid bacilli, colon bacilli or staphylococci, their intramuscular injection in larger dosage, the intravenous injection of bacterial or other protein split products such as proteoses; of colloidal metals; of distilled water or hypertonic salt solution; of various serums and antitoxins; the intramuscular injection of milk or casein, the subcutaneous injection of nucleic acid or sodium nucleate, the production of sterile abscesses with minute injections of turpentine, are all followed by a reaction that varies from a mere stimulation of leukocytes, to mild febrile reactions, and to extreme shock pictures associated with profound vasomotor paralyses. The reaction varies with the substance used, its method of application and absorption, and its dosage; with the type of infection with which we are dealing; with the number of previous injections; with the physical condition of the patient; with the duration of the disease from which the patient is suffering; with the temperature of the patient at the time of the injection and other individual factors.

We do not yet know how much of the reaction that we elicit is necessary to bring about the therapeutic effect that we seek to achieve. We know that some substances provoke fewer symptoms that are uncomfortable to the patient and yet seem quite as efficacious in their result. On the other hand some substances are followed with only a mild reaction and seem much less effective than the methods that are seemingly more drastic in their action and much more unpleasant for the patient.

Certain of the agents always give a reaction in both normal individuals and persons ill from disease and give a reaction in a relatively short period of time after the injection. Typhoid vaccine belongs in this category. The colon bacillus more often gives a delayed reaction, while some of the protein split products such as the albumoses may produce a reaction in diseased individuals but not in a normal person when the same dosage is employed.

Holler, while working with deuterio-albumose in patients, tried its effect on himself over a period of over two weeks. In patients the intravenous injection of 1 c.c. of a 10% solution was invariably followed by a slight drop, then a rise in temperature of from 2—3° C., a chill, occasionally sweating, rarely

an urticaria, etc. When he injected it in himself these symptoms were entirely lacking. He gained in weight during the course of the injections.

This in general has been our experience in normal individuals when we have injected small doses of secondary proteoses intravenously. The reaction on the part of the patient depends to a considerable degree on the amount of bacterial destruction that follows the injection or the amount of necrotic tissue involvement of the patient.

Just how much of the nonspecific reaction is essential, whether the discomfort of the intravenous bacteriotherapy can be modified by using the protein split products without sacrificing any of the remarkable therapeutic effects that are at times achieved, is not to be determined at present but must be the subject of further clinical investigation. For purposes of orientation we have in the following pages described the reaction that follows the intravenous injection of typhoid bacilli in moderate dosage—25 to 50 million organisms; not because it may be the ideal form of therapy of this type but because it is the reaction which is most familiar clinically and, because of the availability of the vaccine, the most easily obtained agent for experimentation.

It is practically impossible to ascertain beforehand, because of the varying individual factors, the degree of the reaction that will be produced. When, however, experience has been gained with a definite preparation and with a certain class of clinical material it is usually possible to gauge the results that are to be expected with some measure of exactitude. Needless to state it is an elemental precaution to begin with a small dose when undertaking a study of the effect on patients.

**The Chill.**—Usually the first symptom that comes to the attention of the patient following the injection is a chill or rigor. This may set in as early as fifteen minutes after the intravenous injection of typhoid bacilli or a proteose solution, usually within 30 minutes, but may be delayed for several hours. When colon bacilli and some other organisms are used the chill may not be observed for several hours, in one of our cases not until 8 hours after the injection. With intramuscular milk injections the rigor commences in from two to three hours.

The degree of the reaction varies—there may be merely twitching of the leg or arm muscles, or the chill or rigor may be quite general and severe and last from 20 minutes to an hour. Commonly this phase of the reaction begins to wear off in from one-half to three-quarters of an hour after its inception.

During this time the patient may complain of actual sensation of chilling and demand extra covering and hot water bottles; in other cases there is merely the muscular twitching and trembling without sensory disturbance. In the acute arthritides this phase of the reaction may be of considerable discomfort to the patient because of the added motion and its resulting pain in the involved joints.

The analgesic effect that follows shortly in the wake of the chill as a rule compensates for this short period of increased pain.

**The Temperature Curve.**—The temperature reaction of the patient varies greatly with the vaccine or protein used, and even when one adheres to a single agent such as typhoid vaccine, differences in the age of the vaccine, the dosage, the strain of bacilli and the method of killing the bacteria when the vaccine is prepared, all have a definite effect on the reaction; and this apart from the individual variation that we meet on the part of the patient—variations that depend, as already mentioned, on the disease, its duration, the previous temperature, previous injections, etc.

With the subsidence of the chill or during its later stages the temperature of the patient has as a rule commenced to rise. In typical arthritic cases running a febrile course of from 100° F. to 101° F. the injection of typhoid vaccine will raise the temperature to about 103° F. or 104° F., the maximum increase being recorded in from three to four hours after the injection. With intramuscular milk injections the temperature maximum may not be reached until six or eight hours after the injection. As a rule the defervescence is more rapid with the intravenous injections, but even in the case of the milk injections the former level is reached within 24 hours. Subcutaneous nuclein injections are followed by a febrile reaction that begins later and recedes more slowly than observed with the other methods.

Schmidt has classified the reactions following milk injections into 5 groups, according to the degree of febrile reaction of the patient following a uniform amount of milk intramuscularly injected. In the first group are the cases that react with 37° C. or under; in the second that react with 37° C. to 38° C. (98.6°-100° F.); in the third that react with 38° C. to 39° C. (100°-102° F.); in the fourth that react with 39° C. to 40° C. (102°-104° F.); in the fifth that react with 40° C. to 41° C. (104°-106° F.).

Schmidt and Kaznelson worked chiefly with milk injections, using 10 c.c. injected intragluteally. The temperature rise occurred usually in from 6 to 8 hours and was at times accompanied by a chill (rather rare), more often by sweating, and some headache. The blood pressure was not altered. Herpes were seldom noted. The temperature increase at times persisted for from 24 to 48 hours. Among the five groups into which Schmidt and Kaznelson have classified their patients it will be of interest to observe some of the cases in the first three groups. They are as follows:

Temperature under 37° C., Group I	Carcinoma, 4
(98.6° F.) (Normal)	Secondary Anemia, 1
	Myotonia (Thomsen's Disease), 1
	Diabetes, 2
	Influenza, 1

37° C. to 38° C., Group II  
(98.6°-100° F.)

Hysteria, 1  
Achyilia, 1  
Icterus, 1  
Acromegaly, 1  
Chlorosis, 1  
Posthemorrhagic Anemia, 2  
Gonitis, 1  
Polyarthritis, 3  
Chronic Arthritis, 2  
Carcinoma, 8  
Diabetes, 3  
Cholecystitis, 1

38° C. to 39° C., Group III  
(100° to 102° F.)

Tuberculosis, 4  
Gumma, Liver, 1  
Hemophilia, 1

It is of peculiar interest to observe the relative resistance of the carcinoma cases of this series to temperature response following the injections (most of these were stomach and esophageal cases). The reactivity of the neoplasms varies greatly—some observers report rather violent reactions; others, such as Schmidt, believe that they are examples of decided resistance. It seems most probable that the reaction depends largely on the amount of necrosis present in the tumor, its vascularity and its anatomical position. Schmidt correlated this relative resistance to the milk injections with his previous observations concerning the relatively low "Infection Index" of carcinoma patients and their resistance to vaccines. Wetzel believes that the absence of a febrile reaction to parenteral injection of milk is not constant enough to aid in diagnosis, although it is occasionally conspicuous in diabetes and cancer.

Schmidt noticed that the reaction was independent of the dosage to a considerable degree, although after one or more doses had been given, the reaction became less marked. It depended to a large degree on the individual, and the type of the disease. Thus in a normal person one can inject as much as 1 c.c. of a 10% solution of albumose without appreciable temperature reaction or constitutional effect of any nature. In an arthritic patient the same injection may raise the temperature two or three degrees; in a typhoid or tuberculous patient by as much as five degrees (F.). On the other hand, when the same dose is injected in a pneumonic patient who already has a high temperature (let us say 103° F.) the temperature may not be increased, or may actually show a decline without any preliminary increase after the injection.

Habetin, using 0.5 gm. of sodium nucleate subcutaneously in a series of some 60-odd patients ill with a variety of diseases, classified his reactions according to the system of Schmidt.

It will be observed that the most marked pyrogenic effect is manifest in diseases involving hematopoietic organs and those in which definite

foci of pathological tissue exist such as sarcoma, tuberculosis, etc. The degree of febrile reaction is independent to a considerable degree of the agent or the dosage; it depends on the infection and the state of the patient, i.e., on an individual factor.

	I	II	III	IV	V
Malaria .....	2	5	4	4	0
Tuberculosis .....	0	2	4	1	1
Acute Arthritis .....	0	2	3	6	0
Gonitis .....	0	1	1	0	0
Multiple Sclerosis.....	0	3	3	1	0
Diabetes .....	0	1	0	0	0
Coxitis .....	0	1	0	0	0
Banti's Disease.....	0	0	1	0	0
Morbus Maculosis Werlhofii.....	0	0	1	0	0
Typhoid .....	0	0	1	3	0
Pernicious Anemia.....	0	0	1	2	0
Chlorosis .....	0	0	1	0	0
Sarcoma .....	0	0	0	1	0
Pyemia .....	0	0	0	0	1
Endocarditis .....	0	0	0	0	1

Gow, who early employed heterovaccines, came finally to the use of the colon vaccine as being most dependable, other vaccines such as streptococcus, etc., being followed by little temperature effect. He noted the fact that the reaction varies greatly in different individuals, just as had Schmidt. A dose of 50 million might in one instance cause a severe reaction but little in another. For therapeutic result Gow concluded that a moderate reaction was essential.

That the injection of bacteria would cause fever and that the reaction depended to some degree on the digestion of the bacteria was noted many years ago. (Gamaléia.) Roux and Lepine had observed the pyrogenic effect of the other protein substances before this, while Charrin and Ruffer determined that the pyrogenic effect of the bacteria was thermostable, that is, they heated the bacterial emulsions to 110° C. and were still able to get the original pyrogenic effect on injection.

The later studies of Buchner, Schittenhelm and Weichardt, of Friedberger, Vaughan, etc., are of course well known.

**The Pulse.**—Coincident with the temperature reaction the pulse is almost invariably increased to some extent, usually about 15 to 30 beats per minute. With the onset of the sweating the peripheral dilatation brings this down to almost the preinjection level. As a rule the quality of the pulse is not altered, and arrhythmia, if present beforehand, is not increased. Cyanosis is uncommon; I have observed it only once following an injection of proteoses in a case of typhoid fever. In this case the cyanosis was a transient phenomenon and the patient

went on to a complete recovery from his typhoid in two days. Cyanosis is but infrequently noted in the literature. Gow has recently studied the pulse rate in patients receiving peptone injections intravenously. He finds that the higher the leukocytosis, the greater the rise in pulse frequency after injections. The increase in pulse rate in his cases varied from 5 to 20 beats per quarter minute. The pulse frequency returned to normal in from 3 to 5 minutes after the injections. With vaccines these effects are of course greatly delayed.

The character of the pulse and its rate is of decided importance in determining which cases are suitable for injection. In typhoid a rapid pulse rate (over 100) is a contraindication to nonspecific therapy. Experimentally it has been shown that small doses of proteoses stimulate the heart muscle, the amplitude and the force of the beat being increased (Weichardt). In several cases of long-standing heart lesions associated with arthritis we have watched the size of the heart after nonspecific injections—both during the acute reaction and the defervescence. In these cases the left border went out about 1 cm. and returned to the preinjection size in from 24 to 48 hours. The patients showed no evidences whatever of any cardiac decompensation. Naturally only cardiac patients that were in good condition were selected for the injections.

**The Blood Pressure.**—Scully was one of the first to undertake systematic studies on the blood pressure of patients after typhoid vaccine injections. It is of course quite difficult to obtain an accurate reading during the time that the patient has a chill, but enough observations have been recorded to indicate that there is a slight increase in blood pressure during this time. When the chill has subsided and the period of perspiration sets in, the blood pressure shows a progressive decline of from 10 to 25 mm., reaching a maximum in from 6 to 8 hours, and returning to the normal pressure within 24 hours. Considerable variation is noted, however, in individual cases, depending on the dosage, the agent used and the infection of the patient.

When injections are given to a typhoid patient in the later stages of the illness, where evidence of an unstable vasomotor system following the long continued toxemia is apparent, we have observed a vasomotor paralysis extending over a period of 48 hours and very refractory to stimulation. In one such case the systolic pressure sank to 55 mm. and remained very low for 24 hours. This patient had been running a very high typhoid temperature for 4 weeks without any evidence of improvement. Following the recovery from the injection his temperature remained normal and the patient made a complete recovery.

A number of factors enter into the effect on the blood pressure. It has been noted for instance that the subcutaneous injection of relatively large doses of typhoid vaccine—Besredka or Vincent—during typhoid fever, while it has a much less apparent effect on the patient in the form of chill, fever and sweating, seems to be

followed by far greater depressing effects on the cardiovascular system than the intravenous injection of small amounts of typhoid vaccine. After milk injections Müller has observed a slight primary decrease, then an increase in the blood pressure.

While the effect on the blood pressure depends on individual factors—the duration of the disease, the agent used, etc., the fall in the blood pressure which accompanies shock effects depends largely on a dilatation of the vascular bed in the splanchnic area. The peripheral dilatation which one can observe with the sweating of the patient does not produce the extreme drop in the blood pressure that the splanchnic engorgement does.

Different animals respond to the injection of protein split products, peptone, histamin, etc., with different effects on the blood pressure, depending on which part of the vascular bed is subject to constriction, on stimulation of the vasomotor nerves, etc. The liver of carnivora responds with a spasm of the capillaries with a resulting diminution of the blood supply to the right heart and a lowering of the blood pressure. The primary effect is followed by a dilatation. The liver of the herbivora is quite indifferent, indicating a difference in innervation. The spasm of the arterioles of the portal area results in a passive filling of these vessels while in the lungs we have also a contraction of the arterial system with a resulting dilatation of the right heart, accompanied by a fall in pressure in the left heart and the general circulation. In discussing this mechanism Mantner and Pick call attention to the fact that the difference in the effect of the shock poisons in herbivora and carnivora is easily explained by the differences in the behavior of the various capillary systems. Simonds has recently noted this same difference in the behavior of the musculature of the hepatic vein and has drawn conclusions similar to those of Mantner and Pick. Dale's conception of the mechanism does not quite follow that here presented.

It becomes apparent from a consideration of the possible mechanism in the dog and the human after such shock effects why stimulants such as adrenalin are relatively ineffective while vasodilating agents such as caffeine are said to be followed by more effect in the acute stage of shock depending on such vasoconstriction of the hepatic vein and its branches.

The possibility that other factors enter into the change in the blood pressure is by no means excluded. v. Behring laid great stress on the finding of thrombi in the capillaries of the lungs in acute anaphylactic shock and Hanzlik and Karsner have recently called attention to the fact that the intravenous injection of a number of colloids and typical non-specific agents may be followed by such changes in the finer capillaries.

**Sweating.**—Shortly after the subsidence of the chill the patient may sweat profusely; in arthritic patients one finds this most frequently; typhoid and pneumonic patients are less apt to sweat after the injections, but may do so if the injection is followed by an increase in temperature and a critical fall.

A number of observers have claimed that the mere production of a profuse perspiration will relieve arthritic symptoms and a variety of therapeutic procedures have been elaborated which have as their object the production of a sweat, either by applying external heat or the administration of a variety of drugs. There seems little doubt that many patients are relieved to some extent by such measures but there is almost invariably a recurrence of the symptoms after the sweating has stopped for 24 hours. The possible mechanism that is involved in any therapeutic stimulation of the skin such as occurs when the patient is sweated is discussed in the chapter on the relation of the skin to internal diseases.

**Nausea and Vomiting.**—This is occasionally observed after relatively large doses of vaccines or after particularly toxic strains of bacteria. It is usually an indication that the dosage has been too large or that the patient is particularly sensitive. The entire gastrointestinal tract will frequently show increased peristalsis.

**Palpable Spleen.**—Gow has observed that the spleen may become palpable immediately after the reaction.

**Effect on Menstruation.**—Lux has observed that the menstrual flow is augmented after nonspecific injections.

**Nervous Irritability.**—Kling showed some years ago that during the period sensitization following on the injection of some protein parenterally the nervous irritability of the animal was considerably increased.

Following nonspecific injections it has been found that a similar alteration takes place but the effect on the threshold of the nerve reaction is a diphasic one. There is for a short period following the injection a lowering of the threshold for nerve stimuli, clinically demonstrable by the increase in the pain, and the general hyperexcitability. This is followed by a period of lessened susceptibility to pain, somnolence, and the clinical manifestations of the marked euphoria which has been commented on by almost every one who has had experience with nonspecific therapy. Döllken, working with neuritides has observed a similar reaction in the local effect on nerve tissues. He found that after heterovaccine injections there would be a response on the part of the lesion either in a negative sense—increased pain, etc., or as a positive phase—analgesia and complete restitution to normal in some instances.

**Herpes and Urticaria.**—Herpes has been observed to follow a number of intravenous injections. We have noted a labial herpes after use of typhoid and colon vaccines (certain strains seem to be more prone to produce herpes than others). Auld has reported an occasional herpes after intravenous injection of colloidal metals. Gow has observed such eruptions after heterovaccination and they have also been reported after milk injections.

Urticarial eruptions are not so common. We have observed one

quite generalized rash in an arthritic patient that came on within three hours after the injection and had disappeared after 24 hours; other observers also report that skin manifestations are uncommon in their experience.

**Headache.**—Headache of the frontal region is a common symptom following typhoid and colon vaccine injections, but is observed less frequently after milk and other substances. The headache is not as a rule of long duration, lasting usually not more than two or three hours after the chill.

**Delirium.**—In diseases associated with marked intoxication, such as typhoid, typhus and erysipelas, the intravenous injection of non-specific agents may at times be followed by intensification of the disease manifestations and among them delirium may at times be observed. It is usually a very transient phenomenon that disappears as soon as the febrile reaction diminishes; only rarely does one observe any disorientation that persists past the reactive period following the injections. Care must of course be observed in excluding alcoholics from nonspecific injections, for such patients may develop a delirium tremens during the reaction which, once elicited, may lead to a fatal termination. Several such cases have come to our attention.

**Glandular Activity.**—Weichardt has carried out a number of experiments in which he has shown that the injection of moderate amounts of protein split products increase glandular activity. He demonstrated this in lactating goats as well as for the salivary glands of a number of animals. Döllken has reported an increased secretion of bile following milk injections.

The question of the galactagogue effect of parenteral injections of milk, of interest to the pediatrician, has been the subject of considerable investigation, but has not been conclusively settled.

Slawik, during the course of his work with nonspecific injections in infants, had occasion to inject several wet-nurses. Duncan is said to have observed a galactagogue effect after the injection of milk parenterally in lactating women, but Slawik in his cases was not able to confirm this result. Lönne has published observations that indicate an increased secretion of milk after parenteral injections, but his conclusions have been criticized by Kirstein, although the latter does not deny the possibility of glandular activation.

**Nitrogen Metabolism.**—The nitrogen balance shows considerable variation both experimentally and clinically following the parenteral introduction of the proteins and their split products. It is of course beyond the scope of this discussion to examine so-called specific dynamic effect of proteins in their general effect on the normal metabolism after ingestion, although certain facts that have been derived from a study of this field indicate that there are fundamental differences involved in the cellular reactivity incident to the digestion of

proteins as contrasted to the absorption and metabolism of the carbohydrates and fats.

A number of years ago Italian observers noted that in normal animals the injections of small doses of toxins and of tuberculin were followed by an augmentation of the nitrogen metabolism (excretion) followed by a period in which an excess of nitrogen was stored. Animals treated with small doses of tuberculin would gain in weight as contrasted to normal animals without injections.

Much work has been done during the course of studies on anaphylaxis, and inasmuch as this simulates the picture that we obtain in nonspecific therapy to a considerable degree, the results are not without interest in this connection. Schittenhelm and Weichardt noted the immediate increase in the nitrogen excretion in anaphylactic dogs after a shock. Thus one dog from a normal excretion of 1.88 gm. per day excreted 2.8, 3.3, 2.65, 2.41 the days following shock, amounts far in excess of the amount of protein injected to produce the shock. Segale noted the same effect and Manoiloff observed an increased excretion of nitrogen in rabbits despite the fact that the temperature had diminished.

Hirsch and Leschke have studied the same subject in a very thorough manner. They found that with fairly large doses of anaphylatoxin a negative nitrogen balance obtained, whereas smaller doses or mild shocks often led to a positive balance. They noticed that the excretion of nitrogen did not necessarily bear any direct relation to the temperature of the animal resulting from the various pyrogenic agents. Breed's studies are also of interest in this connection.

In the patient the injection of the nonspecific agents with the resulting reaction is associated with an increase in the nitrogen excretion just as such shocks are associated with an increased metabolism in animals. In a number of cases that we have followed the total nitrogen excretion of the urine increased from 20% to 30% above that excreted before the injection. After about two days the nitrogen excretion again reaches the normal and for a variable period after this time there exists in many patients a diminution in excretion.

**The Weight of the Patient.**—Uddgren has followed the weight of a series of patients given intramuscular milk injections. This included 4 groups. In the first were included patients who received "market" milk, with rather severe temperature reactions. In the second were those who received alternating doses of either "sterile" or market milk. In the third group were those who received a series of injections of either the one or the other. In the fourth group were patients who received the "sterile" milk entirely. The results were as follows:

I. Usually some increase of weight during course of injections. More often a slight decrease followed later by an increase.

II. Well marked increase in weight.

III. Usually slight decrease during first series of injections, later an increase.

IV. Little if any alteration. In a few cases a well marked increase in weight.

In this connection we must keep in mind the possibility that such changes in weight as here observed may be due to alterations in the water balance of the tissues, rather than an actual increase in tissue substance.

**Albuminuria.**—According to all clinical observers the injections are not followed by any alterations in the urine that would indicate an irritation of the kidney parenchyma. The only exception to this general statement is the effect that at times follows the intravenous injection of colloidal metals. With these it has been observed that after the subsidence of fever (in influenza) the injection may at times be followed by the reappearance of casts and some albumin in the urine if they had been present at the time of the acute illness. In this case the agent seems able to activate a low-grade inflammation which may still be present.

Uddgren observed no kidney irritation in about 100 cases injected with milk. In only two cases was a trace of albumin noted after the injections and this was a purely transient phenomenon. v. Aaron, who examined the disposal of casein injected intravenously in animals, found that 58% of it was excreted through the urine, a fact that must be considered if traces of albumin are reported in the urine after milk injections.

On the other hand, several observers (Döllken, Schmidt, etc.) have reported that when nonspecific injections are made during the course of an acute illness accompanied by albuminuria and casts in the urine, the urinary findings clear up very promptly after the injections. Döllken noted this particularly in his patients ill with Weil's disease where a high-grade albuminuria cleared up immediately after the injections.

**Diuresis.**—Injections are frequently followed by a diuresis of some extent. Riedel has called attention to this fact.

**Permeability of the Blood Vessels.**—Luithlen in 1912 studied the effect of the intravenous injection of various substances, such as serum, gelatin, starch, and crystalloids, on the course of the common skin reactions and as a result of his preliminary work investigated the permeability of the capillaries after such injections. His method consisted in injecting Ringer's solution into the abdominal cavity of rabbits, then following with the intravenous injection of the agents that he wished to study, then determining the permeability of the abdominal capillaries by injecting sodium iodid and also sodium ferrocyanid intravenously and testing the rate at which these substances had entered

into the fluid in the peritoneal cavity. The colloids depressed the rate; crystalloids increased the permeability when studied under these conditions. Similar studies were made by von den Velden.

Siegert as well as Schmidt studied particularly the effect of protein injections on the smaller vessels. They found that small doses increased the permeability, while large doses decreased the rate. The most recent studies are those of Starkenstein. These were carried out by producing corneal ulcers in rabbits and then observing the rate at which dyes (sodium fluorescein, etc.) would diffuse out at the site of the lesion after a variety of nonspecific injections. Apart from milk, albumoses and collargol he tried out a large number of drugs including quinin, atophan, salicylates, adrenalin, methylene blue, iodine, etc. According to his observation practically all these substances were followed by a diminution of the permeability of the capillaries and he accounts for their antiphlogistic effect on this basis.

From the effect noted on the lymph system and the experiments on the capillaries above described it seems very probable that the effect of the nonspecific injections is to increase the permeability of the capillaries for a short period and later to cause a definite lessening of the permeability. The reaction and the direction of its maximum effect will depend largely on the dosage employed and to some degree on the agent used.

**The Lymphagogue Effect.**—It is well known that certain substances, which Heidenhain classified as lymphagogues of the first class, among them peptone, egg albumin, tissue extracts, etc., cause a marked increase in the lymph flow, supposed to be derived largely from the liver (Starling). This increased flow may continue a considerable time following such injection. Teague and McWilliams have recently advanced the explanation that this lymphagogue effect is responsible for the therapeutic effect of protein injections in that the antibodies of the blood stream are forced into the lymph spaces and there destroy the invading organism. Davis and Petersen investigated this effect on the lymph flow, using large dogs in whom a lymph fistula was established at the thoracic duct and then injecting killed colon vaccine intravenously to produce the shock effect. When necessary small doses of morphin were given. If the animals were injected too soon after the operation and before complete recovery had been made from the anesthetic, considerable resistance to the shock was manifest and the temperature reaction was delayed for several hours.

**Lymph Volume.**—The increase in the rate of the flow of the lymph followed immediately upon the injection and in severe intoxications two periods of maximum flow occurred, the first immediately after the injection and persisting for from 20 to 30 minutes, the second after approximately 1 hour, the latter increase being continued over a longer period of time. When the intoxication was not so great the

two-phase curve did not occur, the increase being less in extent but persisting for a longer period of time. (Fig. 1.)

*Concentration of the Lymph and Serum.*—The concentration of the lymph proteins following the injection is considerably increased, as determined by the Kjeldahl method for total protein nitrogen, while the concentration of the nonprotein nitrogen may decrease.

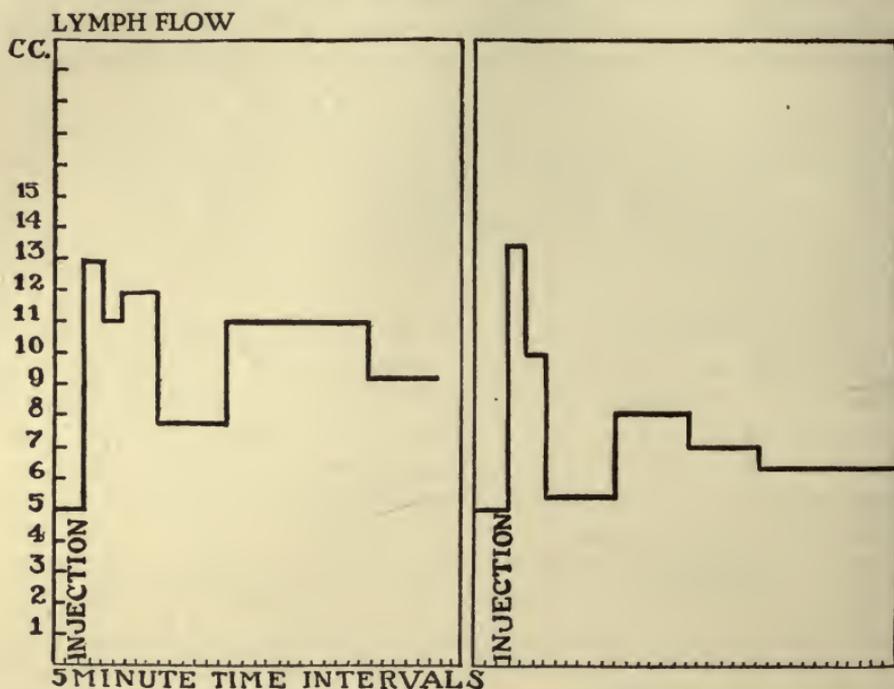


FIG. 1.—Volume of lymph flow following *Bacillus coli* vaccine injection.

**The Leukocytes.**—Few of the changes following nonspecific therapy have received the study or attention that the leukocytic reaction has. The earliest workers with nonspecific methods of treatment followed the leukocytic picture with great care, particularly because some of the earlier methods—the fixation abscess, yeasts, nuclein injections, colloidal metals, etc.—were developed at a time when clinicians began to pay considerable attention to the leukocytic count.

The rôle of the leukocyte in immune processes is by no means an exhausted field of research; indeed it is one that in many ways seems to offer an exceptionally attractive approach to innumerable problems still obscure. Nägeli in his "Blutkrankheiten" surmised that a leukocytosis that resulted as an expression of an immune reaction on the part of the bone marrow might be of decided therapeutic use. Fiessinger and Marie have for many years emphasized the importance of the enzymes of the leukocytes in infectious disease while the work of Metchnikoff and his pupils has so thoroughly covered the general field of phagocytosis that it will be unnecessary to enter

into a subject that is so well known and the literature of which is so accessible. The discussions in Zinsser's "Infection and Resistance" give a comprehensive idea of the subject.

The experimental production of a leukocytosis, and the study of the leukocytosis that is produced after the injection of a variety of substances of bacterial, protein or chemical derivation have been carried on for a considerable period and inasmuch as the results are quite comparable with those obtained in the human it may be well for a moment to consider the present status of our knowledge of the subject.

The effect of the injection of bacteria and bacterial extracts on the leukocytes was studied experimentally by a large number of investigators. Lange, injecting typhoid bacilli in rabbits, noted that after large doses there was an immediate leukopenia that was later followed by a recovery and a leukocytosis, in one of his cases going to 43,900. Polymorphonuclears were found to predominate, with transitional and large mononuclear cells appearing later. He observed the presence of normoblasts as well as a polychromatophilia; myelocytes were also noted. Goldscheider and Jacob using staphylococci observed a similar reaction, although the reactive leukocytosis did not reach the extreme degree that Lange found. Schlesinger using streptococci could only determine a leukopenia. When typhoid bacilli were used for a repeated series of injections Hirschfeld found that the bone marrow became atrophic. Studer studied the effect of typhoid and coli toxin on the leukocytes and Friedlander using staphylococci observed that with these organisms he obtained a maximum leukocytosis with relatively no leukopenia preceding it. Samson-Himmelskjerna, one of the earlier observers, noted a leukopenia after peptone injections.

Andrews found that the colon bacillus produced the greatest leukopenia in rabbits, staphylococci and diphtheroid bacilli less than colon bacilli. He was of the opinion that in immunized animals there was a more pronounced reactive leukocytosis than in normal animals.

Gay and Claypole in their work on the mechanism of recovery in typhoid fever reported studies which seemed to support the contention that in immunized animals the leukocytic response on reinjection was greater than in normal animals and that this was a specific reaction. McWilliams was not able to confirm these findings. It is very probable that as a result of sensitization the whole organism becomes more responsive and will react more readily and more intensely to a reinjection, but recent work such as that of Bieling would rather indicate that to a considerable degree it is immaterial what the agent is which is injected, as long as it has an irritant or stimulating effect.

Schittenhelm, Weichardt and Greisshammer went over this phase of the reaction of animals to bacterial and other proteins and came to the following conclusions:

The intravenous injection of native protein, peptone and bacterial protein causes in the dog an immediate leukopenia depending not only on the size of the dose but on the character of the agent. Native protein pro-

duces such a leukopenia only after sensitization, peptone with the first injection. Among the bacterial agents the typhoid bacillus when injected produces the most persistent leukopenia; some varieties of tuberculin, colon bacilli and staphylococci also have the same effect. On reinjection the leukopenia becomes less marked in degree and duration. The authors suggest that this effect is due to a functional paralysis or depression of the bone marrow. It is probable that in a great part the peripheral leukopenia so observed is due to the accumulation of the leukocytes in the internal organs—spleen, liver, etc. If the injected dose is too large the animal of course dies in this shock or depression stage.

The stage of leukopenia is followed by one of leukocytosis which persists for from three to six days; the degree of the reaction is diminished on further injections. Of the bacterial injections typhoid and staphylococci produce the most marked leukocytosis.

This reactive leukocytosis that follows is of myeloid type—that is, of neutrophile polymorphonuclears, large mononuclears and transitional types. Eosinophils are at times also increased. The lymphatic apparatus is relatively passive.

The protein split products and the bacterial proteins also stimulate the hematopoietic system, as indicated by the appearance of normoblasts, megakoblasts and polychromatic reds in the days following the injection.

Two or more factors enter into these changes that have been observed in the relation of the leukocytes after nonspecific injections. The leukopenia that follows immediately is due to an accumulation of the leukocytes in the internal organs—lungs, spleen, liver, gastrointestinal tract and the bone marrow. Dale is inclined to the belief that because of changes in the intima of the capillaries and smaller vessels the leukocytes tend to adhere to the walls and therefore do not appear in the circulating blood. The leukocytosis that follows the leukopenia is a reactive phenomenon due to a stimulation of the bone marrow. Andrews followed the Arneeth count and found that the neutrophils with undivided nuclei outnumbered the divided ones. The presence of bone marrow cells of various types after the reaction was further evidence of the stimulation of the marrow.

During the height of the reaction the leukocytes are more actively phagocytic than normally, the ingestion of erythrocytes by the polymorphonuclear leukocytes being observed after typhoid injection.

That a leukocytosis followed the subcutaneous injection of nucleins was noted when they were introduced about thirty years ago; Bauer studied the leukocytosis that followed the fixation abscess and a similar reaction on the part of the leukocytes was observed to some degree after serum injections, after the intravenous injection of colloidal metals, following autoserotherapy, etc.

With the development of nonspecific therapy and the endeavor to find a satisfactory theoretical basis for the therapeutic results obtained, a number of investigators naturally turned to the study of the leukocytic reaction and its possible bearing on the problem. Some believe that the chief factor in the therapeutic result lies in the leukocytic stimulation, others see merely an accessory factor in

the leukocytic response, still others deny the leukocyte any rôle in the mechanism of recovery by nonspecific methods. The problem is one of considerable importance and it may be well to consider the facts that have been reported.

Scully studied the leukocytosis in some detail. In his arthritic cases treated with typhoid vaccine injected intravenously, the injection was first followed by a leukopenia (the leukocytes dropping from an average of 14,000 to about 5,000), following this the process would be reversed and a leukocytosis make its appearance. This would frequently reach 30,000 or 40,000; in one case the count was 62,000. When subsequent injections were made the reaction was usually less marked.

In the primary leukopenia Scully found that the absolute number of polymorphonuclear leukocytes decreased, rising later from the normal of about 60% to over 90% of the total. Scully found that the large mononuclears were decreased during the first three hours, but after that again maintained their normal proportion. The lymphocytes were relatively and absolutely decreased, as were the eosinophiles, although these latter at times showed a slight increase later.

Rohonyi found that the leukocytes increased following typhoid vaccine injections but that the leukocytosis bore no relation to the therapeutic effect obtained. He also noted that there was some increase in eosinophiles. Gow also studied the blood cytology in the cases that he treated with heterovaccines and peptone injections. He observed the primary leukopenia which involved all elements and noted that after one hour the polymorphonuclear leukocytes still outnumbered the lymphocytes but that from that time on the young forms of neutrophils became more abundant (the neutrophils with undivided nuclei outnumbered those with divided nuclei). After 72 hours he was of the impression that preinjection conditions were restored. During the height of the leukocytic reaction his counts averaged from 20,000 to 30,000 and myelocytes and normoblasts were to be observed.

Holler and Weiss studied the leukocytosis that was to be observed after milk injections, as did also Schmidt and Kaznelson. The latter observers found a very slight increase in the eosinophiles after the first stages of the reaction had subsided. Their observations on the lymphocytes would lead one to believe that the effect on these blood elements was more protracted than Gow's observations would indicate. They state that they were increased over the normal for a period of several days after the polymorphonuclear leukocytes had reached preinjection figures.

Schmidt and Kaznelson have grouped the leukocytic reaction that follows parenteral milk injection into three classes. They observed first a group in which a primary leukopenia was followed by a leukocytosis consisting largely of polymorphonuclear neutrophils. In

a second group, in which a leukocytosis was already present (as in leukemias) the injection was followed by a decrease in the number of neutrophiles. In the third group the reaction consisted chiefly in an increase in the number of mononuclear elements.

Müller has emphasized particularly the myelocytic stimulation that is brought about by milk injections. While the lymphatic apparatus was practically unaffected, myelocytes were thrown into the circulation in abundance, indicating a marked stimulation of the bone marrow.

Recently Nagaó has studied the cellular changes that follow the intravenous injection of killed nonhemolytic streptococci into guinea-pigs. Most of the cocci were taken up in leukocytes within five or ten minutes, and cocci could be found in circulating leukocytes for as long as three hours. The cocci and polymorphonuclear leukocytes accumulate in the lungs during the first ten minutes, and it is here that most of the cocci reach the interior of the phagocytes. At the same time there is a general leukopenia, and the polymorphonuclear leukocytes of the spleen are reduced to about one-fourth the normal number. There is a similar reduction of such leukocytes in the bone marrow. After thirty minutes the lungs are nearly normal, the number of leukocytes in the blood may be normal or increased, and there is a beginning accumulation of the leukocytes in the liver and spleen. There is also a marked proliferation of the endothelial cells of the liver and spleen, and of the leukocytes of the bone marrow. In from two to three hours there is a marked accumulation of leukocytes with ingested cocci in the liver and spleen, the number of leukocytes in the blood is increased, and immature leukocytes appear in the blood and bone marrow, indicating an exhaustion of the leukocyte-forming power of the marrow. It is suggested by Nagaó that the reaction of a patient to vaccine treatment may be determined in some degree by frequent examination of the blood, the appearance in it of immature leukocytes indicating danger of exhaustion of leukocytogenic centers in the marrow and elsewhere.

Cowie and Calhoun in this country made a detailed study of the leukocytic reaction following intravenous typhoid injections. They observed the primary leukopenia and found that the maximum reaction took place between the 4th and the 9th hour after the injection, their leukocyte counts then ranging about 30,000. The polymorphonuclear cells which appeared were new cells with large nuclei. Large lymphocytes frequently disappeared at some time following the injection. The small lymphocytes never wholly disappeared although they were greatly decreased, in one case to 200 cells per c.mm. The transitional cells were usually below normal in number while the eosinophiles were not increased. They observed the appearance of great numbers of myelocytes which were to be found sometimes within

one-half hour after the injection and in one case reached the total of 800 cells per c.mm. Among these basophiles were frequently observed. Nucleated red cells, both megaloblasts and normoblasts, were also observed. Türck irritation forms were also noted (acidophile granular lymphocyte forms) and irregular small lymphocytes. Cowie and Calhoun consider that the leukopenia is due to an emigration of the leukocytes to the internal organs. According to their observation they obtained the most satisfactory clinical results in those patients that responded best with a high leukocytosis.

Holler, on the other hand, does not consider a leukocytosis an essential factor in the therapeutic result. Lüdke as well as Holler noted a slight eosinophilia after the albumose injections.

Other nonspecific agents produce a leukocytosis of varying degree and studies have been made on the blood cytology following injections of serum, nucleins, colloidal metals, salt solution, turpentine, iodids and a number of related substances. (Pfenninger; Hammett, Kessler and Browning; Paaschen; Fiessinger and Marie, etc.)

Müller considers that digestion leukocytosis represents merely the leukocytic reaction to the protein split products absorbed during the course of digestion.

**The Erythrocytes.**—Schittenhelm, Weichardt and Griessheimer observed the erythropoietic irritation that followed a variety of bacterial injections, just as other observers before them had noted the presence of many nucleated red cells after such intravenous injections. Clinically it has been observed that the red count is increased after nonspecific injections in anemia; in pernicious anemia the increase is as a rule transient and uncertain.

**Platelets.**—Duke has observed that small doses of typhoid vaccine increase the number of blood platelets while larger doses cause a diminution in the number. Cowie and Calhoun report that the platelets after typhoid injection increase in number and size. Döllken, on the other hand, found no constant alteration in the platelets after milk injections although he found a decided styptic effect from such injections in cases of hemorrhagic diathesis. He concluded from his observations that the platelets were probably not concerned in the alteration in the coagulation rate.

**Blood Sugar.**—Löwy observed a very prompt increase in the amount of blood sugar following nonspecific injections. (Milk.)

**Fibrinogen.**—The amount of fibrinogen in the blood is increased in about 6 hours after milk injection and remains at a high level for a period of about 8 days. (Löwy, von der Velden.) Moll observed the increase in fibrinogen after the injection of gelatin and serum.

**Thrombokinase.**—Thrombokinase is increased very shortly after milk injections. Deutero-albumoses, bacteria and colloidal metals have little effect on the coagulation mechanism.

**Serum and Lymph Enzymes.**—During the course of a series of studies on the alterations in serum enzymes in animals after anaphylactic shock, after the intravenous injection of protein split products, of bacteria, of kaolin, of trypsin, etc., Jobling and his associates established the fact that as a result of these various injections the animal responded with a mobilization of proteolytic enzymes as well as of lipases. Diastase was not altered to the extent that the other enzymes were changed. The increase in the titer of the protease was very striking after severe intoxications such as those produced by typhoid or colon bacilli.

In view of the fact that the flow of the lymph is markedly augmented and dilutes the blood and that the blood volume is greatly diminished after shock because of the increased permeability of the vessels (Dale has recently observed a diminution of the volume by as much as 40% after histamin injection), Davis and Petersen studied the enzymes of the blood and lymph separately after intravenous injection of colon vaccine. The results of these experiments were as follows:

*Protease.*—The effect of the bacterial shock on the protease content of the lymph and serum was marked in extent. Three types of reaction could be distinguished: (a) the fluctuations in titer may occur simultaneously, (b) those of serum may precede those of the lymph, and finally (c) there may be no relation of the one to the other.

*Peptidase.*—The fluctuations of the peptidase, or ereptase titer, do not parallel those of the protease; indeed the curves may be quite dissimilar. As a rule the increase makes its appearance later than that of the protease and is less extensive. When alterations in titer do occur they appear almost simultaneously in both the lymph and serum, although in a few experiments the ferment was first to be observed in the serum. It is at any rate apparent that the entrance into the blood stream can be direct and does not need to take place via the lymph channels, although under normal conditions, i.e., feeding, this seems to be the one portal of entry.

*Lipase.*—While the increase in this ferment occurs in both lymph and blood following shock, it seems to make its appearance first in the serum.

In the patient the effects of nonspecific injections on the enzymes are not as marked as they are in experimental animals. In a study of serum alterations in patients after nonspecific therapy, Petersen followed the changes to be observed in (a) the stalagmometric readings, in (b) the total nitrogen of the serum (concentration of the serum), (c) the noncoagulable nitrogen, and the titer of the enzymes, (d) protease, (e) ereptase, (f) diastase and (g) esterase.

The results were as follows:

- (a) There was a concentration of the serum.
- (b) The nonprotein nitrogen was practically unaltered.
- (c) The serum protease almost invariably decreased after the shock but later increased progressively for a period of from three to four days.

- (d) The serum peptidase usually increased in the cases that responded with clinical improvement.
- (e) The diastatic activity of the serum usually diminished.
- (f) The lipolytic activity of the serum showed no constant alteration.

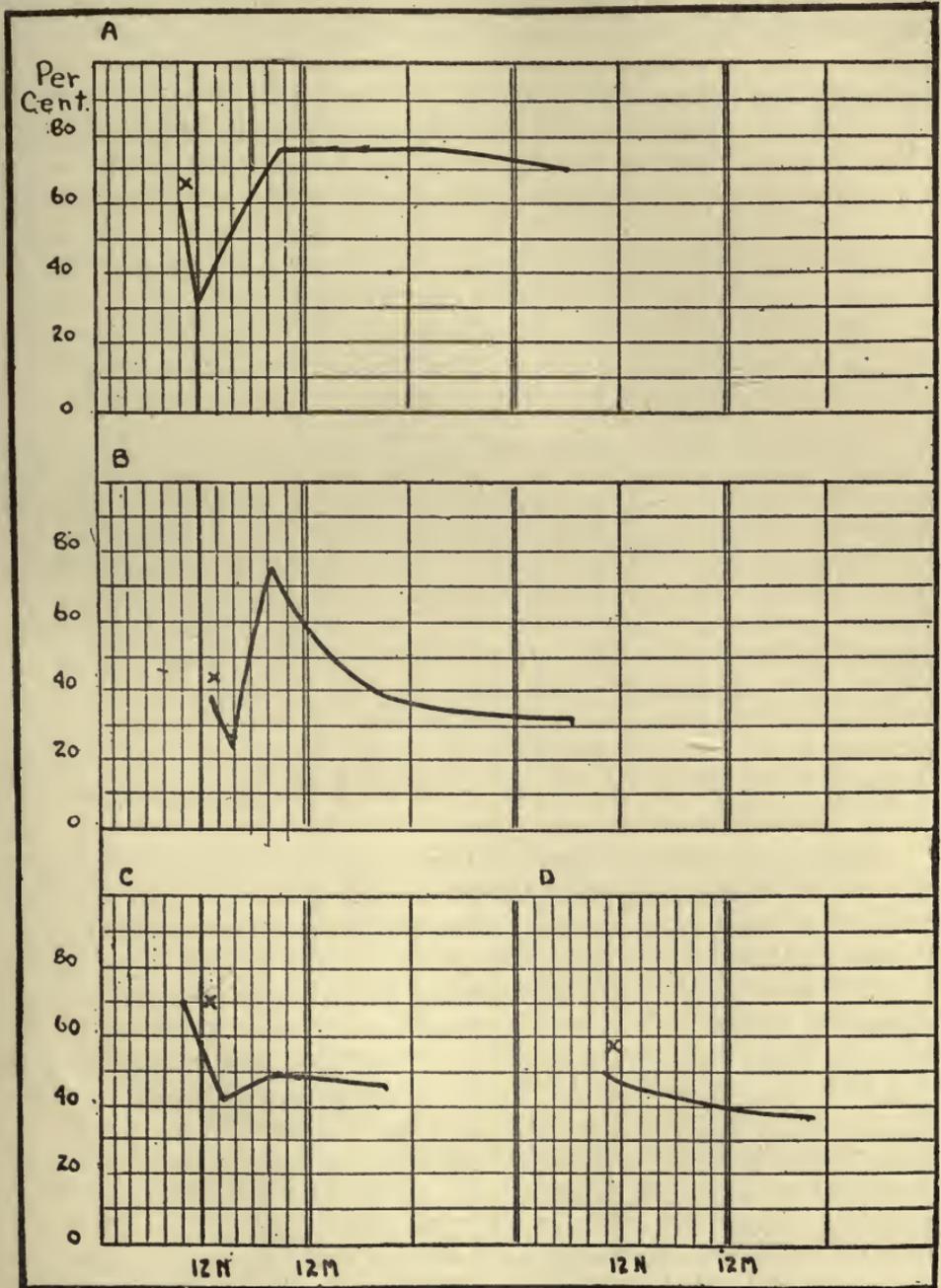


FIG. 2.—Changes in antiferment titer following protein shock. X indicates injection.

**The Antiferment.**—In the course of studies undertaken several years ago Jobling and Petersen presented evidence that seemed to indicate very strongly that the anti-enzyme (antitrypsin) of the serum consisted of the finely dispersed lipoids which contained unsaturated carbon bonds in their chemical structure. More recent research has in general confirmed the view that the antienzyme is lipotropic and not related to the proteins although it may physically be closely bound to some of these serum constituents.

In animal experimentation Jobling and Petersen determined that there was an increase in the antiferment after practically every form of shock to which the animal was subjected—anaphylactic, bacterial, protein, etc. Clinically it had been observed that the antiferment was increased in cachexia, during acute febrile diseases, in pregnancy, after vaccine injection, serum sickness, etc.

In the patient injected with vaccines intravenously the fluctuation in the antiferment titer were followed by Petersen and the types of reaction are illustrated in the accompanying chart (Fig. 2).

“The changes in the antiferment of the blood serum are usually well marked and quite uniform in the cases that react favorably to the shock therapy. Chart A illustrates the changes taking place for a three-day period of observation in a case with complete recovery from an acute arthritis following intravenous injection of 60 mg. of a primary proteose. The persistence of the increased antiferment titer may be much less in duration, as shown in the Chart B. This case, K. H., was one of multiple subacute arthritis which did not improve to any marked extent after injection of typhoid vaccines, although there was temporary relief.

“Finally, the cases that show no permanent improvement seldom show any increase in the antiferment, indeed almost always present a decrease in the titer following the shock, as illustrated in the third and fourth charts, C and D.”

**Antibodies.**—With the introduction of modern methods of nonspecific therapy immunologists turned naturally to an investigation whether or not the therapeutic effect of the injections might not be due to some alteration in the antibody titer of the serum of the patient. As a matter of fact the effort to increase antibody production by stimulating the organism in a variety of ways is by no means a recent subject of experimentation. Thus Solomonsen and Madsen found that if horses were immunized with diphtheria toxin and then injected with pilocarpin the titer was much higher than before the pilocarpin injections. Obermeier and Pick, using 5% and 10% peptone solution for injection, found that animals sensitized three months previously responded with a marked increase in precipitins after the injections. Dieudonné immunized rabbits with typhoid bacilli and then injected hetol and observed a decided increase in the antibody titer. Similar observations have been recorded for nucleins, for colloidal metals and for paraspecific serum injections.

Hektoen, working with rabbits sensitized long before to horse serum, found that when at a subsequent period the same animals were injected with some other variety of serum, the animals again yielded the specific horse agglutinin first formed. This flushing out of a specific antibody under the stimulus of some other and quite different protein has been suggested as a basis of the therapeutic effect of nonspecific therapy.

Thus Müller and Weiss thought that this was the explanation of their results in the treatment of gonorrhoeal complications with gonococcus and other vaccine, but serological tests failed to confirm this view. Ichikawa assumed the same basis for his experiments in typhoid.

Experimentally the results of Conradi and Bieling, and Bieling deserve much interest in this connection, indeed the facts brought out in Bieling's recent paper would seem to have a direct bearing on a number of important questions in infectious diseases. Conradi and Bieling treated rabbits with typhoid bacilli and determined the titer of agglutinin. They then injected colon, dysentery and diphtheria bacilli and observed the same increase in agglutinins that has been described in Hektoen's paper. Bieling has continued these experiments and has found that animals sensitized to dysentery are able to form antibodies against typhoid bacilli when only minute doses of typhoid antigen are injected into them. The sensitized animals can elaborate specific antibodies when only a minute fraction of the amount of the new antigen that would be required in a normal animal is injected. In other words, the first immunization leaves the animal in a state of nonspecific hypersensitiveness during which it is much more reactive to stimuli of all kinds.

The results of these experiments which have been confirmed and extended by Pinner and Ivančević have their direct bearing on the problem under consideration and aid in explaining some of the divergent observations that have been recorded by clinicians after nonspecific injections. We may expect that if injections are made in patients who have been previously immunized that they will respond with an increase in the antibody titer of the serum; if they are injected during the course of a disease, antibodies which have been formed in the cells but not yet cast off may be "shed" as Larson has suggested, and we may then determine an increase in the serum. On the other hand, if they have been thrown into the circulation during the course of a disease as rapidly as formed, we cannot expect any increase in the titer. We may also assume that with the stimulation of the cellular activity ("plasmaactivation") the cells will respond by producing an increased amount of antibodies if they are still capable of such response.

Baluit found that in typhoid patients injected intravenously with typhoid vaccine, there was no definite alteration in the antibodies

unless perhaps an increase in the opsonins. The agglutinins and bactericidal substances were not increased.

Lüdke found the complement somewhat decreased but found that there was no consistent increase in antibodies. v. Groer as well as Svestka and Marek observed no increase in agglutinins after the injection of "typhin" in typhoid patients. Döllken, using milk, noted that the injections did not alter the titer of dysentery agglutinins in patients ill from dysentery. When he used a specific vaccine he did observe an increase of these antibodies, but clinically there was no difference in the effect on the disease whether milk or specific vaccine was used. Reibmayr also found no changes in the agglutinins following the injection of typhoid vaccines.

Flechseder, on the other hand, observed an increase in agglutinins after albumose injections in typhoid patients, while Parlavecchio found an increase in agglutinins and in complement after the injection of nucleins. Borchardt determined that organ extracts (adrenalin, spermin, thyroid, etc.) increased the agglutinin titer of experimental animals, in one case from a titer of 1:20 to 1:5120 and in another case from 1:1280 to 1:12,240.

Culver's investigations are perhaps the most extensive in this field. The opsonins and bactericidal substances were studied in the serum of sixteen patients suffering from gonorrhoeal arthritis. An injection of killed gonococci or proteose solution was given intravenously every seventy-two to ninety-six hours until three to five injections had been given. The serum was taken for study just before each injection. Ten of these patients received successive injections of proteose and six received killed gonococci. No marked difference was seen in the results of the two groups.

His conclusions are as follows: "Primary and secondary proteose preparations stimulate antibody production or mobilization for specific organisms in gonococcal arthritis, in a manner not to be distinguished from that produced by the injection of the specific organisms themselves.

"In gonococcal arthritis, there is either no change or a decrease in the antibody content of serum within the first twenty-four hours following an intravenous injection, in all excepting the first injection when the lytic substances seem to be slightly increased during this time.

"In favorable cases the first injection usually causes the greatest clinical benefit. However, refractory patients may give a similar lysin increase during the first twenty-four hours following an injection; hence the subjective and objective improvement in favorable cases cannot be unquestionably attributed to an increase in antibodies alone. However, little as these substances may have to do with the early relief of symptoms in gonococcal arthritis, it may be

that they have considerable to do with the final recovery from the infection by their influence upon the primary focus."

Culver observed that both the opsonic and bacteriolytic titers of the serum of patients suffering from gonococcal arthritis were normal or below normal before any injections were made. This has been previously observed by Irons and others for the opsonin content of serum from these patients. Irons also demonstrated that spontaneous fluctuations in antibody content occur in gonococcal arthritis and that by massage of the affected joints or the infected prostate there resulted an opsonin increase not altogether unlike that produced by an injection of killed gonococci. Culver believes that any antibody change which results from an injection of a substance which produces a chill might well be explained by the motion of the affected parts during the chill. But since the curves regularly show an increase in lysin and a decrease in opsonin after the first injection and reaction, while each succeeding injection is usually followed directly by an antibody decrease regardless of the intensity of the reaction, it does not seem that the joint motion has much to do with it here. The above antibody changes occur in serum of patients with acute, subacute, or chronic joints with no appreciable difference between these classifications. Some serums were studied after a small amount of protein was injected, large enough to increase the leukocytes and temperature but not sufficient to produce a rigor. These injections were followed by antibody changes not unlike those produced by the more severe reactions.

**The Effect on the Wassermann Reaction.**—Uddgren found that following milk injections, Wassermann negative luetic patients frequently became Wassermann positive. Zeisl finds that gonorrhoeal patients after an injection of "Gonargin" or "Arthigon" may give a positive reaction. This observation is related to that of Strickler, Munson and Sidlick who found that after salvarsan injections non-syphilitic patients may become serologically positive. Conradi and Sklarek have also observed changes in the Wassermann reaction after intravenous injections of typhoid vaccine.

## CHAPTER IV

### THE FOCAL REACTION

In the preceding chapter the changes that take place in the organism after nonspecific injections have been discussed in detail. We will now have to consider a related subject of utmost importance from the therapeutic as well as the theoretical standpoint, namely, the focal reaction that becomes evident about inflammatory foci after nonspecific injections. Just as the general symptomatology of the patient may be accentuated after the injections, so it has been observed that preëxisting inflammatory lesions, endogenous or exogenous in origin, will very frequently become more acute, with an apparent increase in pain, tenderness and hyperemia. This increased reaction is usually followed by a diminution of the objective evidences of inflammation until in many instances a complete restitution to the normal is brought about. In order to understand the possible significance and therapeutic importance of this phenomenon it will be necessary to briefly review our present conception of such focal reactions.

Ever since the tuberculins were introduced early in the nineties the concept of the focal reaction, the "Herd Reaktion," at the site of the inflammatory lesion has been so closely associated with the diagnostic and the therapeutic principles of the tuberculin as hypothesized by Koch that the field has been limited largely to a consideration of this particular disease. This view of the focal reaction, exemplified, let us say, in a local disease such as lupus or an apical involvement, needs no further elucidation. By some the term "local reaction" is, however, used synonymously; it should of course be reversed for those reactions that occur at the site of the injection of the tuberculins.

By common consent we may assume that positive local and general reactions are regarded as corroborative evidence that at some time the organism has been infected with tubercle bacilli; to the focal reaction we generally attach greater significance in so far that the observation of the focal reaction following tuberculin injection is regarded as proof not only of infection but of activity as well. It is regarded as strictly specific in the sense that only tuberculous processes respond to tuberculin injections. On this assumption the

immunologists have elaborated theories to picture the processes going on at the site of the reaction. According to Wassermann and Bruck the reaction takes place when the injected tuberculin joins with an "antituberculin" at the focus and the complement is bound by these two reacting bodies. The fixed complement is then able to "digest" the focal material and so cause the well-known lytic phenomena that we associate with focal activation. Wolff-Eisner and others have expressed the idea that all the tuberculin manifestations are due to preformed specific "lysins." These break up the nontoxic tuberculin; only the tuberculin so altered can initiate the various reactions. The entire mechanism, according to the humoral views, depends on the presence of lysins—i.e., "much lysin—much reaction."

As a matter of fact little or no evidence has been put forward to support this humoral theory, but, on the contrary, much convincing evidence discrediting it. No antibodies of the kind hypothesized have been demonstrated. Nor does a parallelism exist between the local, focal and general reactions, such as would be predicated if the reaction were a humoral one. On the contrary, while a general reaction follows in the wake of a focal reaction, the local reaction is under these circumstances suppressed. But practically every clinical phenomenon has, nevertheless, been interpreted according to these theories with resulting confusion. One illustration will suffice. Menzer noted that tuberculous foci would respond with a typical "Herd Reaktion" after the injection of a streptococcus vaccine and that tuberculous patients would very frequently have a general reaction. From this he drew the conclusion that such reactions merely indicated that a secondary infection with streptococci had been imposed on the focus and that the evidences of reaction which he observed merely confirmed the specific concept.

As a matter of fact it was through the demonstration of the focal or "Herd Reaktion" that the theory of specificity for the tuberculins gained wide credence. We fitted a theory to the observation and then proceeded to interpret every clinical observation in this or the related fields to conform to our theory. Reasoning in a vicious circle retarded the study of actual clinical conditions and particularly held back the proper recognition of certain factors in cellular resistance which are of great importance not only in tuberculosis but in inflammation in general.

Inasmuch as experience with tuberculosis is common to every physician, the consideration of the focal reaction in the tuberculous is perhaps of greatest interest and importance, but the problem is so closely bound up with inflammatory reactions in general that it may be permissible to include certain references to conditions of non-tuberculous origin in this discussion.

**Concerning the Specificity of Focal Reactions.**—Perhaps the fact that the focal reaction is not a specific reaction must first be emphasized. Practically every inflammatory focus, irrespective of its etiology, will react (focal activation) to tuberculin as well as to a great variety of other agents, chemical or biological in character. Investigators in tuberculosis have long recognized the fact that the tuberculous lesion responds with a focal reaction to a variety of substances. Baldwin mentions nucleoprotein, nuclein, albumoses, cinnamic acid, cantharidin, pilocarpin. Fishberg adds potassium iodid and creosote. But the recognition that nontuberculous inflammatory foci will likewise respond to such agents has only been discussed in recent years. Perhaps the paper of Schmidt is of greatest value in this connection.

Schmidt began his observations on the Poncet type of arthritis. This tuberculo-toxic form of disease exhibits a well-marked focal reaction following the injection of tuberculin—that is, the joint becomes more painful, and swollen, there is an increased limitation of motion and the tissues become hyperemic. This stage is later followed by improvement in the clinical picture (the negative phase is followed by a positive one), the end results usually being an improvement over that obtaining before the tuberculin injection.

But Schmidt found that if instead of injecting tuberculin, milk was used, he obtained exactly the same reaction at the site of the lesion, during the same period of time, and with the same positive phase following in the wake of the reaction (i. e., a therapeutic effect). Further, when he turned to nontuberculous joint lesions and injected minute doses (.001 gm.) of Old Tuberculin (relatively rich in nonspecific proteins) he obtained a similar focal reaction.

**Classification of Focal Reactions.**—The German clinicians have gathered considerable data concerning the reactions that follow milk injections (used merely as a convenient nonspecific protein) and Schmidt has arranged the following groups in which there is a response with a typical focal reaction following milk (and other) injections:

- I. Inflammatory foci of infectious origin.
- II. Localized inflammatory processes endogenous or traumatic in origin.
- III. Diatheses.

**I. INFLAMMATORY FOCI OF INFECTIOUS ORIGIN.**—Classified under the first group we include *pulmonary foci of tuberculous origin*.

Schmidt and Kraus, Petersen, Holler, Döllken and others have called attention in recent papers to this phenomenon. Proteoses, iodids, milk, nucleins and other agents will bring about a focal re-

action and a sharp general systemic reaction. *Tuberculous foci in lymph glands*, in the *kidney* and the *genito-urinary tract* and elsewhere respond in a similar manner. Closely related we find the effect on *leprous lesions*. Josephson describes the activation of a case of macular leprosy following the accidental injection of a relatively large intravenous dose of vaccine.

Among the nontuberculous inflammatory foci can be included the *tonsils* which at times flare up after a nonspecific injection. Schmidt describes such a case in which a milk injection activated a latent angina with the coincident appearance of mild joint pains. Inflammatory activation can be observed following milk injections in cases of *furunculosis* and in some instances more than the usual amount of constitutional reaction. Thus the normal diabetic does not react with a temperature rise to milk injections, but if suffering from furuncles will frequently do so. We also note *arthropathies*, the negative phase of which, with its increased pain, swelling and limitation of motion, is not an uncommon clinical observation and has been fully discussed by a number of observers. Inflammatory foci in the *appendix* and the *gall-bladder*, *erysipelas*, *inflammatory lesions of the eye*, *inflammatory lesions of the respiratory tract*, of the *female adnexa* and the *male genito-urinary tract*, etc., are also found. Schittenhelm observed that following the injection of typhoid vaccine old fistulas would show an increased amount of secretion; bronchiectatic patients would secrete more mucus; chronic appendiceal lesions would become more painful and tender, etc.

The activation of quiescent *malarial foci* has assumed diagnostic importance and will be more fully discussed. *Papules of syphilitic origin* react with an increased hyperemia just as do other inflammatory foci.

In a general way one can make the statement that any circumscribed inflammatory process irrespective of its bacterial etiology or its location will frequently light up with a typical focal reaction after a nonspecific injection and usually within 24 hours after the injection. Of these various processes tuberculous lesions are perhaps more sensitive because of a more profound sensitization of the tissue cells of the host *against* protein in general—as suggested by a recent discussion by Wolff-Eisner.

II. LOCALIZED INFLAMMATORY PROCESSES ENDOGENOUS OR TRAUMATIC IN ORIGIN.—In this category must be placed certain of the *toxic forms of arthritis*, such as the Poncet type, as well as *gout*. *Inflammatory lesions of the kidney*, and *inflammatory lesions of the eye*, including iritis, albuminuric retinitis, etc., are also among the localized processes. *Healing fractures*, such as Döllken has described, respond with a typical focal reaction. Neuritis is to be included in this group.

III. LOCALIZED LESIONS ON A BASIS OF A DIATHESIS.—Using this term in the broader significance as defined by Pfaundler, the following conditions might be included:

The *lancinating pains of tabes* which at times follow on nonspecific injections, as well as an occasional gastric crisis.

In *paresis* the psychic state may be decidedly disturbed and the disease manifestations become more apparent following nonspecific injections. This is not an uncommon experience in the treatment of paresis as outlined by v. Jauregg. In *epilepsy* an attack may be inaugurated if a large dose of a nonspecific agent is administered (Adrenalin-Benedek), just as in chronic alcoholics an attack of *delirium tremens* may follow such an injection.

In this sense we may consider that a latent symptomatology may abruptly unfold its various manifestations following injections of protein.

**Activating Agents.**—We must for a moment stop to consider the agents that are involved in eliciting this nonspecific reaction. Because of the early work in this field we commonly regard the nonspecific reaction as one that follows the intravenous injection of a vaccine—let us say typhoid vaccine, or such protein derivatives as proteoses, or more recently the use of milk (given intramuscularly). Not only do such injections bring about the reaction and the focal activation, but certain general biological alterations such as coincident but remote disease processes, metabolic alterations of endocrine origin, fatigue, intestinal intoxication, blood-letting, Roentgen exposures, trauma, alterations in the skin, chilling,—counterirritation—as well as certain drugs bring about exactly the same focal alteration. The activation of a tuberculosis by an angina, a remote trauma, the menstrual cycle, by influenza or measles; the provocation of a malarial paroxysm (the result of a splenic focal activation) by an intercurrent disease, by prophylactic vaccination, by severe fatigue, long railroad journeys, overheating, exposure to intense light, chilling or drenching, dietary fault, alcoholic excess and the various other factors that the experience of the war has brought to light; the focal reaction about latent arthritic lesions which Pemberton has described after irradiation, radium, thyroid extract, excitement, etc.; the classical activation of gonorrhoeal processes by a variety of seemingly remote causes; the precipitation of lancinating pains or a tabetic crisis following a “cold”; the origin of a delirium tremens following a trauma; the onset of pellagrous symptoms after exposure to sunlight; these are but a few examples of a universal phenomenon heretofore commonly observed but not recognized as having a common background.

It is very probable that many puzzling clinical manifestations and unusual features of certain diseases may readily be explained

and will appear in a very simple light if we keep in mind the basic idea that the particular symptom complex under study may be due solely to the activation of an inflammatory focus of exogenous or endogenous origin in the manner of the "Herd Reaktion." Many of the curious metabolic disturbances at times associated with diabetes and nephritis can readily be accounted for on such a basis. Even pharmacological study reveals evidence of this same nonspecific effect on inflammatory lesions. Thus the commonly observed Jarisch-Herxheimer reaction (the flaring up of syphilitic skin lesions under specific treatment) is an example,\* while the activation of a tuberculous lesion after iodid medication is an even older observation. So, too, we may get an ulcerative catarrhal condition when a uremic colitis is carelessly treated with calomel, while Königer, in a recent paper, has even been able to demonstrate that the anti-pyretics, when given in proper interval doses, all bring about a nonspecific "plasmaactivation" and must therefore be included among those agents potentially capable of bringing about focal reactions.

This widening of the concept of the focal reaction makes it of decided importance in the special pathology of internal diseases. Acute conditions may often be nothing more than the exacerbation of heretofore latent processes of definite bacterial etiology or perhaps of a diathesis. On this basis can be explained the fact that children often respond with a severe angina to a fault in the diet; that an appendicitis will become acute following an angina, a remote trauma or an injection of a prophylactic dose of vaccine; that a gastric crisis or lancinating pains will commence after some remote exciting cause or an asthmatic attack occur under the influence of some meteorological or climatic alteration.

In many ways this basis for the immediate etiology of an appendiceal inflammation or the flare-up of a gall bladder seems more rational than the suggestion that we deal with a specific localization of bacteria, so altered in their metabolic demands and peculiarities that they will grow only in certain tissues. This latter hypothesis which Rosenow has developed ignores the fact that in the history of acute inflammatory processes one may note a preceding history of remote trauma or systemic shock of some kind or a metabolic disturbance of nonbacterial origin just as often if not more frequently than a history of a preceding infection.

**The Diphasic Character of the Focal Reaction.**—While in the preceding pages the attention has been centered on the fact that a variety of agents may be used to elicit the tuberculin reac-

\* The so-called sensitization of the skin to metallic colloids is similar in character. Hift found, for instance, that if he injected electrargol intravenously after having injected small amounts into the skin previously, the involuted skin papules would again flare up.

tion (focal) one can also determine that nontuberculous processes respond with a focal reaction to tuberculin. Schmidt illustrates this with two convalescent cases of polyarthritis which had been free from fever and local symptoms, pain, etc., for over two weeks. Both cases on receiving 0.001 gm. O.T. subcutaneously, responded with severe pain in the joints previously involved, slight periarticular swelling and some limitation of motion; the duration of the reaction was of course transient. I have had occasion to repeat these observations of Schmidt's and in a considerable percentage of the cases studied I have found that the observation holds true. In processes that can be observed at the exterior surfaces of the body, particularly in the violent activation of chronic inflammatory lesions, one can observe the dualistic nature of the reaction—and this is of paramount importance in the therapeutic application of the reaction—a negative phase in the sense that the tissue is altered more from the normal than heretofore, i.e., the evidences of inflammation are increased—pain and swelling augmented, function impaired, etc.; then a positive phase during which there is a progressive diminution of the inflammation until the preinjection status is again reached or passed, the balance swinging in this direction until practically normal conditions are restored. Augmentation of the inflammation is followed by a diminution until healing is accomplished—the pendulum swings from one side to the other in the wave-like curve that we find expressed so commonly in many biological processes—in the opsonin curve, the antiferment curve, in the leukocytic response, in the coagulation mechanism, in cell permeability, all indicative of the exquisite lability of the balance that exists in living protoplasm.

The focal reaction has its counterpart in the general reaction of the patient that usually accompanies the reaction, occasionally in the tuberculous, more often in acute infections and corresponds obviously with Weichardt's period of "plasmaactivation." This duality observed in both the focal reaction and the general reaction is of utmost therapeutic interest.

It is reasonable that we would seek to make the negative phase, representing an augmentation of the inflammatory process as short as possible and the positive phase relatively intense and protracted. But the possibility arises, based on clinical observation, that the degree and extent of the positive phase (curative) is closely dependent upon and correlated with the negative phase, i.e., that their relative intensity is proportional. We may conceive the negative phase, which in point of time always precedes the positive one, as an exogenously produced irritative process, the positive one, on the other hand, as an endogenously prepared, more or less physiological process of vital repair. Clinically, as far as focal reactions are concerned (as for instance in tuberculosis), it is chiefly the negative phase that comes to our attention in the form of the activation phenomena with which

we are familiar. But, from analogous studies in focal reactions elsewhere it must be assumed that, with proper dosage, the positive phase and the increased tendency to healing follows about the lung focus just as it does about a joint lesion that can be objectively studied. In this duality of the reaction lies the usefulness of the focal reaction as a therapeutic measure.

**Mechanism of Focal Reaction.**—**VASCULARIZED INFLAMMATORY FOCI.**—During the course of the past five years we have become familiar with the biological alterations that take place in the organism after tuberculin injections as well as after the so-called nonspecific agents. These changes, described in the preceding chapter, are numerous and complex but the more important can be placed in two groups: (1) those that deal with cellular stimulation, and those (2) that result primarily from alterations in the permeability of the cells.

The former have been broadly included by Weichardt under the term "Plasmaactivation." Under the stimulus of moderate doses of nonspecific agents cellular activity is markedly increased. This finds its expression in increased secretory activity of gland cells, increased activity of muscle cells (myocardium), increased activity of leukocytes (phagocytosis), etc. The changes that take place in the permeability of the cell membrane have been studied by Luithlen, by Starkenstein and others and represent a decidedly diphasic phenomenon. The permeability of the capillaries is first increased as evidenced in the great increase in the lymph flow and in the concentration of the blood; the permeability of the tissue cells is increased—with a resulting outpouring of enzymes, of fibrinogen and prothrombin, of immune bodies, etc.; the increased permeability of the nerve cells is associated with a lowering of the threshold for nervous impulses and becomes manifest clinically in increased susceptibility to pain, general irritability, headache, etc. When this first phase has passed compensation takes place in a lessened permeability of the cells, with effects that are to be anticipated—lessened susceptibility to intoxication, lessened nervous irritability—lessened exudation—a lowering of enzyme concentration, etc.

Numerous other observations have been made that are, in my opinion, subordinate in interest to these two fundamental alterations in the permeability of the cell membranes and the general stimulation of the protoplasm.

With these considerations in mind we can approach the study of the mechanism possibly involved in the focal reaction about inflammatory tissues from a relatively simple point of view.

In an inflammatory focus supplied with highly vascularized granulation tissue the systemic effects of a tuberculin injection or the injection of a nonspecific agent will bring about (1) an increase in the exudation of fluids—with increased redness and swelling because

of the transient increase in the permeability. With this there is associated (2) an increase in pain and tenderness both because of the increased pressure and the lowering of the threshold or nerve stimuli. There will be (3) increased digestion at the focus of inflammation; if there is no necrotic material present in the focus there may be no evidence of increased systemic intoxication; if the amount of necrotic material is large there will first result an increase in systemic intoxication when the material split down is absorbed; with more complete digestion at the focus, complete detoxication may result.

All these changes we associate with the focal activation that follows nonspecific injections. To these must be added another factor and one more complex. It concerns the observation that any cell previously involved in an inflammatory reaction responds to stimuli of all kinds more readily than a normal cell. Objectively we can observe this in involuting skin lesions.

The augmentation in the inflammatory reaction which we have induced brings with it, as we have seen, an increased lymph flow. Coincident with it there has been a relative increase in enzymes—protease, ereptase (peptidase) lipase, etc.,—an increase in the antibodies (if the patient has been previously immunized or if the infection has existed for some time), an increase in the leukocytes (after the initial leukopenia), together with an increase in their phagocytic activity, and an increased coagulability of the blood. The antibody, the leukocytic and the enzyme alterations must exert a considerable effect on an infecting agent as well as on the removal of necrotic material; the tendency toward restitution to the normal would be enhanced. It is this phase that we see in the so-called second or positive phase. Its coincident constitutional effect that we witness in the euphoria, in the lowering of the temperature, improvement of the circulation, etc., is due to at least three factors—(a) the destruction of toxic material at the focus after the primary increase in digestive activity, (b) lessened susceptibility of the cells of the body to intoxication (due to the lessened permeability), and (c) actual protoplasmic stimulation (partly from the nonspecific or specific agent injected, partly from the toxic material liberated from the inflammatory focus). This later factor varies greatly and the clinical estimation of the possible degree of this variation requires experience and care.

**TUBERCULOUS FOCI.**—Turning from the vascularized inflammatory focus to the tubercle we find other conditions. In Schmidt's paper the view emphasized is that in the general tuberculin reaction we are most likely dealing with both specific and nonspecific factors, an opinion similar to that which we have expressed in a previous paper. Schmidt has stated this concept as follows "But it is probable that in the question of specificity or nonspecificity, the placing of the one versus

the other is a mistake—that it should rather be the examination of specificity *and* nonspecificity, i.e., that both factors enter into the reaction and it should be determined how far each factor is involved.” Our concept has been that while the systemic reaction was largely nonspecific in that the means used to elicit it need not be specific, the focal reaction itself, once initiated, brings in its wake a truly specific stimulation because the inflammatory reaction may lead to the liberation of disintegrating bacterial material and possibly even living bacteria. These substances would secondarily lead to a specific response on the part of the body.\*

At least three factors must be considered in the mechanism of the focal reaction in tuberculosis, apart from the anatomical peculiarities of the tubercle as contrasted with other inflammatory processes.

*Specific.*—These concern primarily a tissue sensitization against tubercloprotein, strictly specific in character, cellular in its localization and not necessarily associated with the older conception that was built up about the humoral antibodies. Indeed I am of the opinion that the latter may very well be relegated to a subordinate position in the field of tuberculosis. Inasmuch as this subject of tissue sensitization has been extensively discussed by a number of workers, particularly by Krause in this country, it will be unnecessary to enter into this phase here.

*General Hypersensitiveness of the Tuberculous.*—Granted that the tuberculous focus responds to smaller doses of tuberculin than does a focus of nontuberculous origin, how are we to account for the fact in view of the practical avascularity of the tubercle? That the specificity concept of the immunologist will no longer explain the accumulated evidence is to-day acknowledged, and Wolff-Eisner accepts the change in our viewpoint in a recent paper. I can but very briefly enter into the more lengthy theoretical discussion that he presents. He first emphasizes the relation that exists between the diet and exudative diathesis, defining this latter condition as due to the ab-

\* It is this factor that Klemperer in his recent criticism of Schmidt's claims has ignored. Klemperer found that following milk injections in tuberculous patients they did not become resistant to following injections of tuberculin and vice versa. Injections of milk bring about a febrile reaction in a large percentage of individuals; they bring about a focal reaction in only a limited number of tuberculous patients, just as tuberculin injections are followed by focal reactions in an irregular number. If the injection of milk brings about (in the tuberculous individual) a systemic reaction without focal activation, a following injection of tuberculin may still give rise to a typical general reaction. If, on the other hand, a focal reaction results, either by specific or nonspecific means, local tuberculin reactions are suppressed for some time following the general reaction. Klemperer is, however, quite justified both in his criticism of the local reactions reported by Schmidt following milk injections in tuberculous patients and in his views concerning the possible harm from activation of tuberculous foci following milk injections.

sorption of proteins and protein fragments insufficiently degraded in the intestinal tract, i.e., a protein sensitization. He then develops the more or less definite association of the exudative diathesis and spasmodophilia with scrofula; while he does not regard the scrofula as the cause of the diathesis, he inclines to the definition of Feer that "scrofula is tuberculosis on the basis of an exudative diathesis." Wolff-Eisner is inclined to the view that in tuberculosis there is evidence of an exudative diathesis with sensitization against tuberculin and also *against proteins in general*. This latter which is nonspecific and general in character accounts, in his estimation, for many of the evidences of similarity in the clinical course of tuberculosis and those observed in an exudative diathesis. Not only is scrofula "tuberculosis on the basis of a diathesis" but the tuberculous lesion itself, involving as it does the prolonged absorption of partially split proteins from the necrotic foci, may ultimately bring in its train symptoms that are commonly regarded as due to a diathesis. As such he regards the changes observed in the cornea, skin lesions such as the tuberculids, the decided alterations in the reactivity of the sympathetic and central nervous systems to which Moro, Pottenger and Ferranini have called attention. While we have been familiar with the increased nervous lability of the tuberculous individual for a long time, we have failed to grasp the dependence of the increased irritability on the general hypersensitiveness to proteins. Not only does this nervous irritability indicate the close parallelism to the diathesis of the child, the tendency to effusion is also evident in the tuberculous patient—one has but to call to mind the common appearance of pleural, peritoneal and joint effusions. The alteration in the vasomotor stability also finds its expression in the frequent appearance of urticarial eruptions after tuberculin injections.

It will be recalled from the previous discussion of the effects of nonspecific injections on the permeability of vascular endothelium that, depending on the dosage or the degree of irritation (or stimulation if we wish to use that term) there may result either an increase or a decrease in the permeability. We may expect that the effect of the tuberculin (or the living virus) will also find some expression in changes in the permeability in one direction or another. According to Wolff-Eisner we find the clinical demonstration of this experimental observation in the effect of the tuberculous invasion of lung tissue, where in one instance we find an exudative change, in another an indurative process.

*Plasmaactivation.*—The third factor involves the consideration of the effects which any nonspecific provocative agent would have on an inflammatory lesion such as the tubercle; the tubercle would react as any seminecrotic focus of other etiology would react were it not for the fact that the tubercle is practically avascular. Tubercles react to nonspecific injections (or to nonspecific stimuli of other origin) only

when they are of the exudative type or when the connective tissue delimitation of the tubercle is either incomplete or exceedingly labile. It is to be recalled that as one of the results of plasmaactivation proteolytic enzymes appear in the serum and in inflammatory foci and that the polymorphonuclear leukocytes are increased in number and in activity. The augmented digestive activity results in a loosening of the connective tissue defense of the tubercle. If sufficiently intense a typical focal reaction—activation-absorption of necrotic material and systemic reaction—can result in this way, just as after stimulation due to specific tuberculins.

**The Therapeutic Application of the Focal Reaction.**—Schmidt is of the opinion that the local reaction, elicited by means of specific or nonspecific agents (such as milk), is of definite value in tuberculosis, and together with Kraus cites some twenty-odd cases to support his view. While it is of course not to be denied that in a very limited number of cases this may be true, we are of the opinion that the tubercle offers a decided exception to the general rule that the active stimulation of a chronic inflammatory focus is of therapeutic value. We have pointed out that for vascularized inflammatory lesions such stimulation affords a rational method of therapy. In the tubercle we deal with the constant danger that the limitation of the lesions by means of the connective tissue encapsulation may be sufficiently disorganized that an extension of the process and irreparable injury may result. Irrespective, therefore, of the theoretical probabilities that therapeutic focal activation may be beneficial, in the tuberculous lesion it is a hazardous procedure (Lewin). Before leaving the subject it must be pointed out that nonspecific stimulation of the tuberculous patient (not involving focal reactions) has been found very useful both with certain drugs (and these include the commonly accepted ones such as creosote, succinates, arsenicals, etc.), as well as with serum injections such as Czerny and Eliasberger have recently reported. That the milder nonspecific injections seem to have a decidedly stimulating effect on the metabolism of infants has been previously reported. (Plantenga, etc.)

The peculiar therapeutic importance that attaches to the diphasic character of the focal reaction has been previously discussed. Through the existence of inflammatory foci in various organs the omnicellular stimulation by means of the various nonspecific agents (the ergotropic of v. Groer) becomes to a certain extent an organotropic. It is in this sense that we must consider the effect of the treatment of paresis by means of tuberculin injections and similar therapeutic measures. A combined therapy of nonspecific and etiotropic agents may be of value, and experiments in this direction have been reported by Kyrle and Scherber, who have used milk injections in conjunction with mercury in the treatment of syphilis, or the use of milk injections and salicylates in the treatment of arthritis, the use of milk injections and

luminal in the treatment of epilepsy, or the treatment of lupus with tuberculin and salvarsan (the latter in this case serving as the non-specific agent). Our older method of treating syphilis with alternating courses of mercury and iodids made use of this form of a combined specific and nonspecific method for many years; the nonspecific effect of the iodids is, however, not marked; the effect is to be sought rather in the effect of the iodids in facilitating the diffusion of the mercury. If a more active agent than iodids is used the mercurialization of the patient can be very rapidly brought about.

While therefore the local reaction has therapeutic possibilities which should be studied and developed, we must always keep in mind that there are possibilities for harm in the reaction. Just as during a malarial attack a syphilis may flare up (Noel), so a tuberculous lesion may become activated after a salvarsan injection or a prophylactic vaccination. Veilchenblau has described an apoplectic attack (old syphilitic) in a patient who was given an arthigon injection for a complicating gonorrhoea.

## CHAPTER V

### THEORIES CONCERNING THE MECHANISM OF THE REACTION

When the clinical results of nonspecific therapy were first made known we were quite at a loss to account for the results obtained. It represented empiricism pure and simple, and being diametrically at variance with current conceptions of immunity and resistance it was to be expected that scientifically trained physicians would be decidedly skeptical—the more so since the heroic measures at first utilized to bring about the reaction were not without inherent danger. But when, with increasing evidence of clinical success, the importance of the reaction could no longer be ignored we had to seek for some explanation to account for the therapeutic benefit even though we had to recast our entire conception of the mechanism of recovery from disease.

The evidence of the reaction of the patient—the chill, fever, sweat and leukocytosis—might all be assumed to have some bearing on the therapeutic result. We knew from experience that after a severe chill the septic case might have a defervescence and recover from the infection. We knew that an intercurrent febrile course might favorably influence a preëxisting disease process. We knew that a thorough sweat would frequently relieve the symptomatology of many diseases. And the importance of the reactive leukocytosis in resistance and its significance in prognosis had been sufficiently impressed upon us in a number of diseases, especially in pneumonia. But none of these observable reactions on the part of the patient seemed in itself sufficient to account for the striking effect that occasionally followed the nonspecific injections.

In examining the published experience of a number of clinics it was found to be a common observation that nonspecific therapy gave best results if used early in a disease process. It was also noted that the beneficial effect from the reaction depended to a considerable extent on its severity; later injections, to which the patient responded with diminished severity, were less efficacious.

These two clinical observations proved a valuable clew to a partial solution of the mechanism that underlies nonspecific therapy. The fact that the most marked therapeutic effect could be attained early in disease rather than late led to the realization that in injecting the

various substances we were stimulating the organism—late in disease, in an exhausted patient, stimulation would naturally be unavailing. The fact that the degree of stimulation and reaction determined the therapeutic effect was evidence of one of the frequently observable biological balances in which the end reaction (recovery in this case) seems proportionately greater than the stimulus (intoxication).

**Weichardt's Theory.**—Weichardt, whose work with protein intoxication and fatigue intoxication is well known, based his explanation of the nonspecific reaction on these two basic observations and the term "Plasmaactivation" or "Omnicellular Plasmaactivation" with which Weichardt has sought to designate the mechanism involved in nonspecific therapy is perhaps a satisfactory one in that we may include under it the many possible and probable alterations that are inaugurated by the reaction without limiting our conception to any one feature. Bessau has but recently pointed out that the favorable therapeutic action corresponds to Pfeiffer's older conception of means to increase the resisting power of the organism, for Pfeiffer showed that a variety of interventions in acute infections induced an immediate increase in the resisting power.

Inasmuch as few investigators in this field of research have had the experience that Weichardt has had, it may be well to go back for a moment to the fundamental observations that underlie his conception of "Plasmaactivation." Gamaléia, in 1888, had observed the pyrogenic effect of bacteria and noted that the degree of temperature rise produced by the injection of bacteria had an intimate relation to the state of digestion of the bacterial cells. Later Charrin and Ruffer noted that when bacteria were heated to a temperature of 110° C. they still retained this property of causing a rise in the temperature, while other nonbacterial proteins also caused an increase in the temperature (bouillon and organ extracts). As a matter of fact, the observation that such substances were pyrogenic was made previously by Roux and Lepine. Later Buchner worked along the same line, incidentally observing the fact that on reinjection the animal may respond differently than after the first injection (one of the early observations of sensitization and anaphylaxis). Ott and Collmar had tried out a variety of protein split products—albumoses, peptone, and neurin—in the smaller laboratory animals, but had obtained very irregular pyrogenic effects. Then Krehl and Matthes published a series of observations concerning the effect of bacterial and other split products on animals (normal, and sensitized by some infection such as tuberculosis), the results of which have already been discussed. Krehl noticed particularly that the experimental animals varied in their sensitiveness to the protein split products. The guinea pig was most susceptible to deuteroalbumose, the rabbit less so and the dog least, quite the same relation that we find in anaphylactic shock.

Schittenhelm and Weichardt and their associates—Hartmann, Greisshammer, Strobel, etc.—made intensive studies of the temperature curve, the leukocytosis, the nitrogen excretion and general clinical picture fol-

lowing protein injections of various kinds in a variety of animals. The leukocytic picture and the temperature curves have been discussed under their respective sections. They noted among other things that the excretion of nitrogen was markedly augmented when the animal was sensitized and then injected, or when a very toxic protein such as that derived from the colon or typhoid bacillus was injected. The derivatives of nuclear destruction in particular were found to be increased. While the effect on the temperature might be relatively negligible, such injections, particularly in dogs, might produce a change in the leukocytic picture lasting at least a day and an increased nitrogen metabolism that would cover a period of 4 days.

In dealing with protein intoxication Weichardt and Schittenhelm emphasize that the bacterial bodies contain too large a variety of proteins and protein split products to obtain a clear picture; the isolated components had to be studied before conclusions could be drawn. They observed that proteins that were made up largely of monoamino-acids, such as peptones derived from silk, casein, hair or edestin, were practically not toxic to the organism; on the other hand, the diamino rich complexes, such as histones and protamins, were exceedingly toxic. According to Ruppel these are present in particularly large amounts in a number of bacteria. When attached to form some other grouping, as for instance a nucleohistone, the histone becomes nontoxic. Detoxication can therefore take place in the direction of synthesis as well as in the further lysis of the protein complexes. Of course, even on lysis toxic amino-acids may be formed, as when beta-imidazolethylamin is formed from histidin. (Studied by Barger and Dahl, Biedl and Kraus, Schittenhelm and Weichardt.)

From their further studies in this direction, Schittenhelm and Weichardt concluded that the conjugated proteins such as nucleoprotein, hemoglobin, glutokyrin sulphate, etc., were relatively nontoxic, whereas the protein components of these complexes were manifestly toxic (globin, histone, protamin) as indicated by their effect on the blood pressure, temperature, respiration, coagulability of the blood and lethal effect. It is not necessary to add that this toxicity is just as pronounced when the derived protein is homologous in origin. While in general the richness in the diamino-acids of these compounds is paralleled by their toxicity, this is not the only factor involved.

Of exceeding interest is their work with hemoglobin, which, apart from a slight temperature effect, was practically nontoxic. They were, however, able to sensitize animals against it. On the other hand, globin was much more toxic. When conjugated with hemochromogen this toxicity again disappeared. This fact is of particular interest in several pathological conditions, such as malaria, where the appearance of the chill and the high temperature reaction has been ascribed to the liberation of hemoglobin and its derivatives. Cowie and Calhoun on the other hand are inclined to the belief that it is due to protein derived from the plasmodia.

Weichardt and Schittenhelm made the further observation that the continued injection of the proteins that caused a toxic reaction was followed by a definite cachexia and ultimately by death. This protein cachexia seems a fairly constant phenomenon and has been observed by Dold as well.

Weichardt then proceeded to study the pharmacological effects of small and large doses of the various higher molecular groupings of the split products of proteins on individual organs. Small doses were found to stimulate the heart muscles as well as the hematopoietic system, larger doses to reduce the activity. Similar experiments were made on the activation of the mammary glands of goats. A series of goats secreting equal amounts of milk were injected with various amounts of protein split products and the activation of the metabolism, as indicated by the amount of milk secreted, could be studied directly.

As a result of his researches and clinical experience Weichardt has come to the conclusion that when we make use of nonspecific therapy we stimulate all the cells of the organism to greater activity in the production of either specific substances antibacterial in character or merely increase the general resistance to intoxication by speeding up the mechanism of detoxication—either synthetic (the formation of conjugate proteins from the toxic forms) or lytic (the degradation of the toxic fragments to the amino-acids) or in some other way hastening the elimination of the intoxicating material.

In several recent papers he has emphasized a number of points of interest. Thus his general conception that nonspecific therapy is a plasmaactivation—a stimulation of the cell metabolism and function, of physiological effort rather than a pharmacologic alteration in the biological processes leads to a correlation with the problem of fatigue, to which he has devoted a considerable study.

Weichardt, contrary to the theory of Döllken,\* considers this stimulation or activation as omnicellular. The leukocytosis, the increase of oxidation, of catalysis, the mobilization of enzymes and antibodies all indicate a general rather than a localized stimulation of some particular kind of tissue.

This stimulation does not involve any alteration in function. The organism by nonspecific reaction acquires no new method of defense, probably does not overcome infection or intoxication through agencies other than those always at its disposal. But the stimulation represents a summation, a cumulative effort of the defensive agencies of all the organs. And as a necessary corollary it is but logical that we can achieve no therapeutic effect when once the organs have by complete exhaustion been rendered incapable of reaction, as in terminal stages of disease processes or in profound intoxication, etc.

While the stimulation does not involve any new method of de-

\*Döllken considers certain proteins and other agents as selective in character. Thus milk which was found to be more styptic in its effects than vaccines or albumoses, he considers active in this way because of greater stimulation of the liver—mobilization of fibrinogen and thrombokinase—deutero-albumose being more effective in mobilizing antibodies, etc. It seems probable that while selective differences may exist, a general protoplasmic stimulation is the phenomenon which must primarily be considered.

fense, differences in reaction exist between normal individuals and individuals ill, or sensitized. The cell that has been sensitized responds more promptly with a mobilization of protective agents, both specific antibodies as well as enzymes and other nonspecific factors in resistance.

Inasmuch as the subject of cell stimulation is so closely bound up with cell fatigue, Weichardt has schematically drawn up the accompanying classification of the substances and agencies that are operative in cell stimulation and therefore in resistance. (Page 88.)

These agents fall into active and passive groups; the passive ones being such that take something—Weichardt lays particular weight on the paralyzing effect of fatigue toxins—protein split products—from the cell. They are identified by the fact that their activity becomes manifest only when symptoms of fatigue have become evident in the organ, and then the effect can never bring about an augmentation of function over the normal—a mere restitution is the limit of their range. Given good resorption their effect becomes apparent at once, while in high-grade fatigue they fail to change the function to any degree.

With the active agents we deal with a true activation whereby the cells are excited to a high grade of activity, demonstrable not only in fatigued but in nonfatigued cells. The dosage is of importance as Weichardt showed in the experiments on isolated organs and organ systems. The dosage must be proportional to the organ to be stimulated and its condition. Usually a definite latent period can be determined before the maximum stimulation becomes manifest.

Now if we keep in mind this relation of stimulation and fatigue, that small amounts of split products (fatigue toxins) may stimulate to greater activity while large amounts will cause only depression, a common observation of nonspecific therapy—namely the fact that on repeated stimulation by intravenous injections the organism fails to react—becomes intelligible. The stimulation wears off, in severe fatigue the reaction may fail entirely.

Schittenhelm in his recent view of nonspecific therapy calls attention to the fact that the derivation of the protein split product used for nonspecific injections cannot be indifferent to us. Undoubted differences must exist in their physiological properties of stimulation or depression. There is no doubt that chemically defined proteins would be best and some work has already been done in this direction. But it must be kept in mind that while we may use a definite protein complex to begin with, split products will also be produced during the course of the reaction from the metabolites of the body and will enter into the reaction.

The euphoria that follows the nonspecific protein therapy can be observed after a variety of similar procedures, both chemical and physical. It is observed after the injection of colloidal metals and

Nonspecific Activation

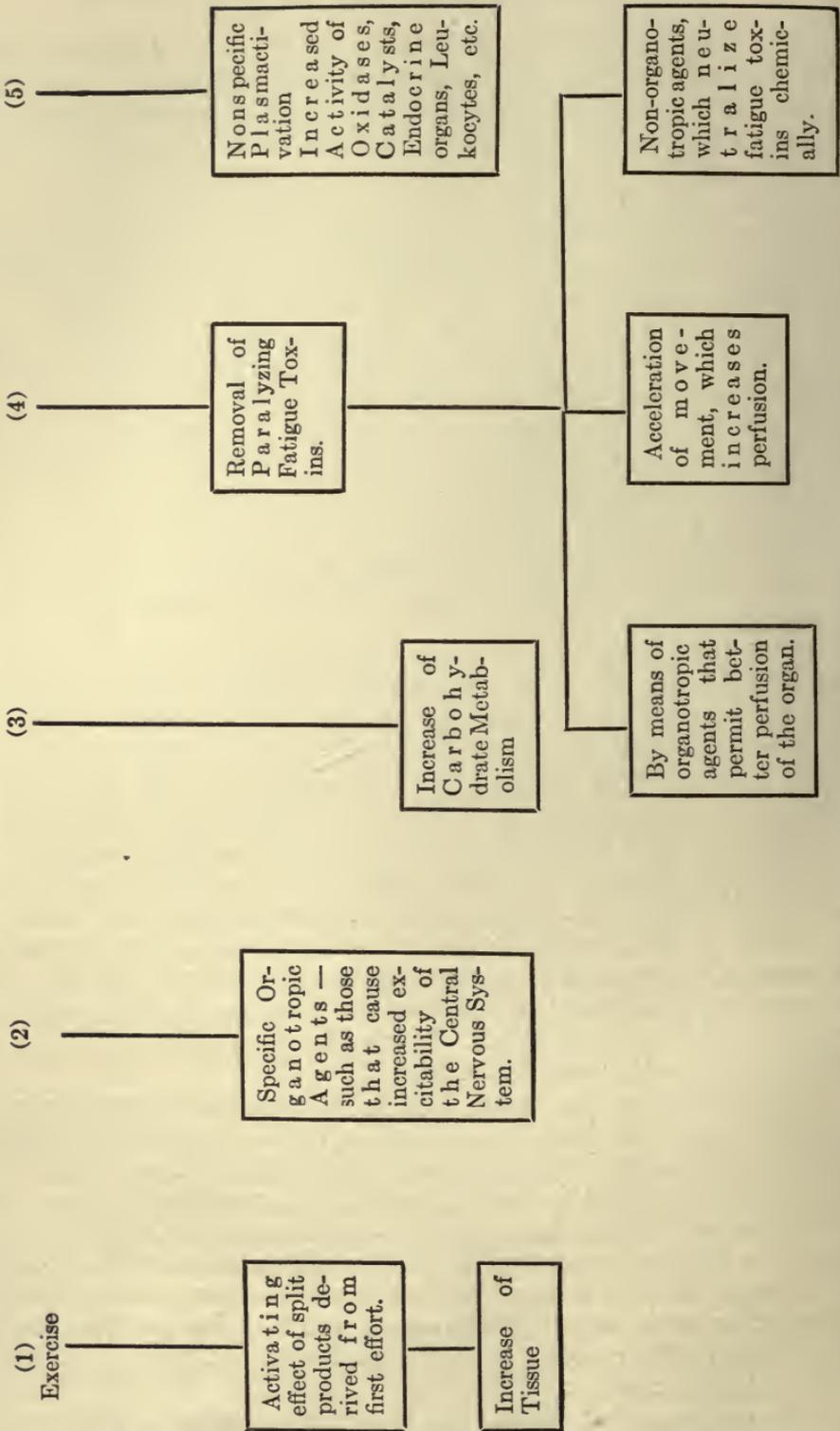


FIG. 3.—Classification of substances and agencies operative in cell stimulation and resistance.

Weichardt calls attention to the fact that a similar state is to be observed after the use of faradic current (Bergonie). Most likely the stimulation of the lymphatic flow whereby fatigue products are rapidly removed is related to this effect.

Schittenhelm and Stroebel a number of years ago emphasized the fact that under normal circumstances protein split products do not get into the circulation, that they are foreign to the blood and their presence would be manifest at once in an intoxication. Protein metabolism, reconstruction and molecular rearrangement and degradation take place within the cell. In this cellular metabolism the protein split products have a dual effect. In small amounts they irritate (stimulate) the cellular activity. In larger amounts they are depressants. Weichardt's "omnicellular plasmaactivation" means simply that we make use of the same agents in proper dosage to stimulate and since we use an intravenous route, all the cells of the organism are stimulated at the same time.

**Selective Stimulation.**—Döllken considers that differences in therapeutic effect exist between the various nonspecific agents, that some of them stimulate particular organs or organ groups and presents a number of observations to support his contention. In several papers he has pointed out differences in effects when various bacterial injections are made—heterobacteriotherapy—thus pyocyaneus vaccines were found effective in gummas, pseudodiphtheria vaccines were not; cholera and dysentery vaccine were not effective in neuralgia, while vaccines made up with prodigious organisms were very satisfactory. On the other hand neither prodigious nor pyocyaneus vaccines gave any clinical result in acne, while an autogenous vaccine did. The effects could therefore not be considered identical. When comparing the styptic effect it was noted that the bacterial vaccines were practically without effect whereas milk was very active. . . . It was interesting to note, too, that while the local reaction at a focus might be equal for two different substances, the end results might be wholly different. Thus both prodigious vaccine and milk gave equal reactions about arthritic foci, but the clinical results with the prodigious vaccine were not good. On the other hand, when treating neuritis the prodigious vaccine gave better results than did milk injections.

Döllken is of the impression that the nonspecific stimulation is not omnicellular as Weichardt has suggested but that certain organs are stimulated by different agents to a greater degree than others, these being the liver, spleen, kidney and bone marrow; a decided effect is also obtained on joints, the tissues of the eye and some of the glands and paraglandular structures. Döllken has made the interesting observation that the effect on joints is not merely a bactericidal one, as might be inferred when an infectious arthritis is improved, but even joint inflammations such as those of gout are also relieved, certainly not a bacterial affair.

Döllken noted that the repeated injections of heterovaccines, milk and similar substances resulted in different reactions. Thus the resistance of the body increases rapidly to further injections of pseudodiphtheria bacilli, to typhoid bacilli and to the bacillus pyocyaneus; the resistance to tuber-

culin and to prodigious vaccine goes up much more slowly. Repeated injections of milk and of deuterioalbumose give rise to steadily augmented temperature reactions, indicating a certain degree of sensitization. Then, too, the fact that following the injection of heterovaccines the euphoria so commonly present after the other agents is seldom noted, also indicated some difference.

It may be well to leave the question whether the plasmaactivation is omniscellular or organotropic and take up some of the other theories that have been advanced to explain the nonspecific reaction.

**Effect on Thermoregulatory Mechanism.**—Paltauf suggests that the effect might be due to thermogenic substances in the vaccine injected. After the stimulation of the heat-regulating center an exhaustion might be expected, as an expression of which he regarded the defervescence after nonspecific injections in acute febrile diseases. This explanation, which Löwy supports, does not take into consideration the frequent permanency of the defervescence.

Saxl considered the hyperthermia as the vital factor which stimulated both antibodies and leukocytes and was also directly effective on the disease process.

Rolly and Meltzer have studied this question. In animals that were infected with a single overwhelming dose of some infectious agent, the effect of raising the temperature was not apparent in the course of the disease process; on the other hand, if the animals were infected with small repeated doses and over a longer period of time it became apparent that by increasing the temperature the infectious process was favorably influenced. The opsonic power of the serum of the fever animals was increased over that of the controls; the bacteriolytic property was not enhanced. There seemed no difference in resistance to pure toxins but Rolly and Meltzer observed that the agglutinin production by the heated animals was increased. Animals that were kept at a high temperature for a period of over 20 days showed no parenchymatous degeneration, but did show a loss of weight and were anemic.

Lüdke has determined that high temperatures *per se* are not damaging factors in infections, for if in infectious diseases the temperature is artificially raised, the disease is seemingly favorably influenced. Lüdke has noticed, however, that on artificially increasing the temperature we may activate latent organisms. He has observed that typhoid bacilli that have (in convalescence) been dormant in the spleen or bone marrow, may again enter the blood stream on superheating the organism, i.e., a hyperpyrexia may at times be a cause of relapse in typhoid fever.

Antibodies that had gradually disappeared after an infectious disease or following immunization artificially produced, were again found in the serum after any procedure that increased the body temperature, whether by increasing the external temperature, influencing the thermal center of the brain or by injecting pyrogenic drugs. Lüdke is therefore inclined to the opinion that the therapeutic effect of hot baths and sweats during the course of any infectious process could be accounted for on this basis

and considered the use of antipyretic substances as illogical, apart from the direct toxicity that they might possess.

Uddgren, as a result of extensive study with milk injections, has come to the conclusion that the hyperthermia is not responsible for the clinical improvement. Working with eye diseases she found that with "sterile" milk the reaction of the patient was very mild but the clinical results were just as good if not better than when market milk was used which gave a severe reaction.

Weiss has applied this theory in the treatment of gonorrhoeal infections with very hot baths. The gonococcus is very susceptible to heat so that it offers a suitable field for trial. He has used baths heated to 42° C. In some instances favorable results have been reported; most patients are not able, however, to stand the treatment (Scholz). (Kapperer.)

**Nolf's Theory.**—Nolf assumes that the mode of action is the following: "Peptone is an easily assimilable antigen. The pathogenic microbes, on the other hand, antigens, are difficult of assimilation. A single mechanism brings about the assimilation of both when they are given by a parenteral route. It is probable that the administration of peptone has the power of stimulating this mechanism and of thus augmenting the destruction of the microbes. As the proteosotherapy is essentially a nonspecific method, it can with advantage be given in association with more or less specific chemical substances when the latter alone are insufficient for bringing about the cure. For this reason I have used proteosotherapy in conjunction with hexamethylenamin in the treatment of typhoid fever, and with sodium salicylate in daily doses of 6 gm. in the treatment of septicemia caused by streptococci and staphylococci and in acute arthritis."

v. Groer believes that we are dealing with an alteration of the entire organism—"eine Umstimmung" or a desensitization, largely due to the loss of the cell receptors, whereby the cell becomes less liable to intoxication. This view will be discussed more fully in the following chapter.

**Enzymes.**—Holler, Lindig, Friedländer, von den Velden as well as Jobling and Petersen have emphasized the importance of the proteolytic enzymes mobilized after the injections. Lindig introduced casein injections on this basis and Jobling and Petersen used proteoses with the same purpose in mind. Lindig's hypothesis has been as follows: The serum of the pregnant woman and the new-born child contains proteolytic enzymes which digest casein; these enzymes are of importance in preventing infection. Other agents may stimulate enzyme action, such as colloidal metals, salt solution, etc., and they have been successfully used in therapy. Lindig considers that the enzymes are heterolytic and that they may be derived either from the leukocytes or from glands. If too large doses of proteins are injected an excess of enzymes floods the serum, tissue-lysis occurs and

the protein cachexia to which Weichardt has called attention may result.

**Antibodies.**—The effect of the nonspecific injections on the mobilization of specific antibodies has been studied by a number of observers. Lüdke had observed that proteose injection would mobilize antibodies in immune animals and introduced proteose injections in patients on this basis. He was not able to determine a constant increase, however, no matter what the clinical result of the injection. In a more recent paper he states that in general the agglutinin titer is markedly increased in the typhoid cases that he had injected, and that there is an increase in the bactericidal property of the serum. As has been stated in a previous chapter the results in this regard are conflicting.

Recently, Larson has published some experimental work bearing on this point. He proceeded on the theory that many bacteria such as streptococci, pneumococci, etc., are imperfect antigens, corresponding to the heated tetanus toxin, the toxoid; that during a streptococcus infection such as an acute arthritis, antibodies are formed against the streptococci, but as this organism does not possess the second stimulus—the exfoliative stimulus—that is necessary to cause the antibodies to be cast off into the blood stream, not sufficient immunity is established to overcome the infection. This stimulus, Larson assumes, is supplied by the nonspecific agent—the vaccine, foreign serum, proteose, etc. In other words, the stimulus necessary to cause the cells to produce the antibodies is specific, but the stimulus causing the cells to throw off the antibodies is not necessarily specific. Using rabbits immunized to sheep's corpuscles Larson found that the injection of foreign proteins greatly augmented the antibody content of rabbits that had only a very low antibody content before the injection. On the other hand, if a rabbit had originally responded with a high concentration of antibodies the secondary injection of a foreign protein did not further increase the antibodies present in the serum.

From these premises Larson draws the conclusion that the injection of foreign protein enables the organism to throw off the so-called sessile antibodies and get them into the circulation. In view of these facts, it is possible that the various agents may act as stimulants of the hematopoietic tissue, thus suddenly flooding the body with immune substances, thereby overcoming the infection. According to Wright, vaccine injections were supposed to be followed by a negative phase, at least so far as the opsonic power was concerned. Contrary to this generally accepted view, Bull has recently shown that this does not hold true following the intravenous injection of a typhoid vaccine in immunized rabbits. Bull noticed that the antibodies were not diminished; on the contrary, they were rapidly increased following the injection. If this is the mechanism involved,

it is important to bear in mind that the stimulus itself is not a specific factor, but that the hematopoietic system has been attuned to respond to a nonspecific stimulus with the production of a specific substance. Larson raises a question in this connection that has occurred to many in the treatment of pneumonia (especially of type I) where some observers claim to have obtained results with normal horse serum equal to those attained with the specific serum. That is, are we dealing with the actual amelioration of symptoms because of the antibodies contained in and injected with the horse serum, or with a nonspecific reaction in which the antibodies that bring about the cure of the patient are derived from the patient under the stimulus of the injection? The fact that Type I serum does not particularly influence Type II pneumonia would speak against the supposition raised by Larson.

As a matter of fact this alteration of the antibody content after the injection of foreign proteins is by no means a constant affair in clinical studies and cannot be considered the sole basis of the therapeutic result. Thus v. Groer found no increase in antibodies after the injections, while Rohonyi found not only that the antibodies, including the agglutinin titer, the bactericidal titer and the opsonic index, were not altered but were at times actually decreased after the therapeutic injection and this despite the fact that the patient was clinically cured. Rohonyi made the further interesting observation that in some of these afebrile typhoids a positive blood culture was at times obtained several days after the injection and after the subsidence of the clinical symptoms. This finding has not been confirmed. (Decastello.)

**Wright's Theory.**—Wright believes that the old conception that vaccines are contraindicated in acute infections because it would be like adding poison to a poisoned system does not apply in infections because immune responses are primarily developed in the infected area and as long as some portions of the body remain which are not involved, these uninvolved portions may be activated by vaccine inoculations for antibody formation to aid the involved portions as a reserve force in overcoming the infection, and that, contrary to previous conceptions, it is found that antibodies are rapidly formed when vaccines are injected into healthy tissues. In this connection he calls attention to the great benefit that was obtained from vaccine inoculations especially in "Poisoned wounds" with streptococcus cellulitis, lymphangitis, erysipelas, etc., and states that the most striking results are obtained when vaccines are employed early in acute cases.

As a means of more clearly expressing immunizing processes, he proposes a series of new terms. Terminology, as now applied in immunology, has a pronounced tendency to confuse the average reader. It is difficult for him to keep the importance of such words like antigen, amboceptor, agglutinins, precipitins, lysins, opsonins, etc., in their proper relations to immunizing processes without a consequent confusion of ideas. He has attempted to clear up this matter by pointing out that in infectious proc-

esses and immunity there are essentially two factors at work; ferment production by the infecting organism for the purpose of preparing the food on which it lives, with the incidental destructive influence on the involved tissues; and tissue produced ferments which have a destructive influence on the invading organisms and their poisonous products. The application of the word ferment is well understood and by pointing out that infection is sustained and immunization established by ferment action, the difficulty of conveying thought through the use of new words is avoided. The substances known as agglutinins, precipitins, lysins, opsonins, etc., may all be regarded on this basis as cell produced ferments exerting varying destructive influences on the invading organisms. This power of cells to produce germ destroying ferments would conform to what Wright calls phylactic power. Kataphylaxis would designate a condition in which cell secreted protective ferments are freely conveyed to the infected area; anti-kataphylaxis would indicate the reverse condition and epiphyllaxis applies to an augmented immunizing activity by calling into operation some reserve immunizing force. Whether these newly coined words will more clearly convey a fixed comprehension of the immunizing process than the terms heretofore employed remains to be seen.

In the application of vaccines much emphasis is laid on the importance of creating conditions by which the immunizing substances are conveyed to the infected area; contending that therapeutic immunization will less frequently fail through faulty conveyance to the infected area than through inefficient antibody formation. This is accomplished by efficient drainage, removing necrotic tissue, instilling hypertonic salt solution, irritating applications, hot fomentations, etc.

Wright's experimental work showing that the bacillus of gas gangrene and tetanus bacilli will not grow in freshly supplied blood serum but will grow freely where the serum is contaminated with streptococci or staphylococci, while streptococci will grow in unaltered serum, is most interesting and shows the importance of removing necrotic tissues and inducing a free flow of blood plasma in these infections. Since streptococci and staphylococci grow freely in blood serum, he calls these organisms serophites. That these organisms are destroyed by leukocytes is most cleverly demonstrated by his glass lath experiment. Here he shows that when the leukocytes are washed with serum, bacterial destruction takes place by phagocytosis, whereas when the leukocytes are washed with normal salt solution, the organisms are destroyed by the mere presence of the leukocyte. Where destruction takes place by phagocytic action it is clearly accomplished by a digestive process and where bacteria are destroyed or inhibited in their growth by the near proximity of the washed leukocytes, this action is necessarily due to some ferment action by the leukocyte. That bacteria destroying properties develop when killed staphylococci or streptococci are added in proper numbers to normal blood, either *in vitro* or *in vivo*, is clearly demonstrated and it is found that this germ destroying power is both specific and nonspecific. This, he contends, conforms to clinical experience and furnishes a scientific basis for obtaining therapeutic results from vaccines aside from their specific immunizing action. This nonspecific action of vaccines also explains the fact that often better results are obtained from the use of stock vaccines than from autogenous prepa-

rations; that in such cases the patient has probably come very near to the end of his tether in immunizing responses to the existing infection when collateral immunization will accomplish the desired results. This he considers very important, because it embraces such a large percentage of cases and says:

"We are, however, here considering primarily the question of principles, and in connection with this what is of fundamental importance is, that we should discard the confident dogmatic belief that immunization must be strictly specific, and that we should in every case of failure endeavor to make our immunization more and more strictly specific. We should instead proceed on the principle that the best vaccine to employ will always be the vaccine which gives on trial the best immunizing response against the microbe we propose to combat.

"I would point out that this would almost certainly not involve any revolutionary changes in the accepted practice in either serum therapy or in prophylactic or ordinary therapeutic inoculation. But it would mean taking into account in cases which proved intractable to treatment with the homologous vaccine the possibility of seeking for collateral immunization by inoculating a microbe or mixture of microbes other than that which the patient is infected."

Wright's work emphasizing the importance of the tissue enzymes in local resistance to bacterial infection is of interest, although we are of the impression that the terms that have been coined by him are superfluous and will merely add to the confusion produced by an already overburdened nomenclature. It would seem much more rational to determine the exact rôle of enzymes already known and for which we possess adequate terms, in the reactions that are involved in tissue resistance; only when we have exhausted this field would it seem justified to bring in new terms to cover hypothetical factors. The antibody reactions should not be confused with enzyme reactions, no matter how much we may be tempted to do so.

Ottenberg and Wallach, who have repeated some of Wright's experiments on the production of nonspecific bactericidal substances by methods described by him, failed to confirm his findings.

**Leukocytosis.**—The reactive leukocytosis that follows nonspecific injections has been repeatedly studied and the suggestion was advanced quite early that the therapeutic effect was to be sought in the artificial leukocytosis established. As noted elsewhere this leukocytosis which follows a primary leukopenia, is largely polymorphonuclear in character; occasionally an eosinophilia has been described (Holler, Rohonyi), suggesting some relation to the anaphylactic picture. It has, however, been the general experience that the therapeutic effect need not parallel the leukocytosis that follows the injections: certain cases respond very favorably as far as clinical results are concerned but show relatively little increase in the white count; in other cases the hyperleukocytosis will be very marked but the therapeutic effect absent. Gay in this country brought out the rôle of

the hyperleukocytosis as a possible factor in recovery from acute infections and considered the reaction specific. This view was not upheld, however, by later workers—Zinsser, McWilliams, etc.

Mueller has studied the leukocytic response in considerable detail and calls particular attention to the fact that myelocytes and nucleated red cells make their appearance very frequently after the nonspecific injections, indicating a very profound stimulation of the bone marrow. On this basis he has recommended and used milk injections in the treatment of secondary anemias. Mueller's results rather support the contention of Döllken that nonspecific injections do not necessarily stimulate the entire organism but may be selective, i. e., acting chiefly on the liver, bone marrow, etc.

**Starkenstein's Theory.**—Perhaps one of the most suggestive and illuminating researches in the field of the mechanism of nonspecific therapy has been that of Starkenstein. Starkenstein would, in the first place, widen the concept of the reaction from that of a protein therapy, or a heterotherapy to one embracing the entire collection of agents—a true nonspecific therapy—including not only the bacterial or protein substances in common use, but the metallic colloids, the various drugs that have been developed such as succinimid, quinin, arsenic, etc., and even purely physical methods. von Groer has covered this in using the term "Ergotropie" to designate this form of therapy.

Starkenstein has been able to show that the various agents under consideration bring about such a change. The method used is a relatively simple and direct one and consists in injecting sodium fluorescein into dogs and watching the permeability of the vessels of the eye to the dye under normal conditions and following the injection of the various nonspecific agents. In a similar fashion the agents were studied in their effect on a keratitis produced by mustard oil. The definite retarding or accelerating action of the drugs on inflammation could be studied in this way. Finally Starkenstein determined the alteration of the toxicity of strychnin and of phenol in dogs that were injected with the agents.

Starkenstein found very definite alterations. Using the dye it was found that distilled water, calcium chlorid, milk and salt injections all altered the permeability of the vessels. A long list of substances was found to be "entzündungshemmend" (anti-inflammatory). This included the following: quinin, ethereal oils, calcium salts, morphin, nicotin, atophan, salicylates, antipyrin, magnesium sulphate, adrenalin, serum, plasma, gelatin, silicic acid, starch, methylene blue, salt, water, fuchsin, iodin.

In the experiments dealing with intoxication Starkenstein calls attention to a fact that a number of Italian observers had previously noted, namely the antagonism existing between toxic substances (Lusini, Lo Menaco, Kleine, Brunner).

A sublethal dose of the one poison will protect to a degree against a toxic dose of the next poison. When Starkenstein tried out the toxicity of strychnin in normal animals and animals previously injected with atophan, milk, or calcium chlorid, the prepared animals were found to be resistant to the poison. With phenol poisoning analogous results were obtained with one exception. While animals injected previously with albumose, atophan and calcium chlorid were more resistant to phenol intoxication, the animals injected with milk were less so. Starkenstein is inclined to the interpretation that this paradoxical result is due to the fact that the phenol is more soluble in the lipoids of the milk and that this lipotropic property brings about a more prompt distribution and the greater activity of the poison.

Clinically Starkenstein noted excellent results by the nonspecific treatment of herpes zoster, venereal complications, eye and ear diseases and erysipelas; in these cases there was at first an invariable increase in the inflammatory process and the local reaction at the site of the lesion, together with a leukocytosis. Scar formation was obviously hastened. Blood sugar was also found to be augmented after the injections.

As a result of these studies Starkenstein concluded that the nonspecific agents have a definite effect on the permeability of the vessels, and therefore on inflammatory processes; that the irritability of the nervous system, both sympathetic and central, seems diminished and that the organism as a result of these demonstrable changes becomes more resistant to such poisons as strychnin and phenol. It is of course known that the irritability of the central nervous system is increased during protein sensitization and diminished after protein shock, obviously conditions analogous to those studied by Starkenstein.

This alteration in the permeability of the capillaries and consequent effect on inflammatory foci has also been studied by Luthlen, by Siegert and by Schmidt who consider it of importance in the nonspecific therapeutic effect.

Rohonyi has suggested that the effect of the nonspecific injections is to produce a neutralizing substance against the invading bacteria and antitoxin. No experimental evidence points in this direction.

Pemberton has suggested another factor that may be involved, particularly in the mechanism of recovery from arthritis after intravenous injection of typhoid vaccine. He calls attention to the improvement that occurs in arthritis after lowering of the food intake of the body, when the body draws on its glycogen store. According to his studies there seems some relation of the glycogen metabolism and the pathological alterations of arthritis. During the reaction that follows intravenous injections there is every reason that we have an

increase in the rate at which glycogen is metabolized, and Pemberton believes that the increased catabolism of the glycogen as well as the incidental low food intake that occurs for the day following the injection may have some relation to the cure of the disease, although it cannot be the sole factor in bringing about the result.

## CHAPTER VI

### THE PROBABLE MECHANISM OF THE REACTION

In discussing the theories proposed to explain the mechanism of the therapeutic processes which we are calling into play when non-specific therapy is used, it will be well for the moment to dismiss the rigid conception of antibody immunity that has been built up on the researches of Ehrlich and the contemporary French and English workers, not because it is unimportant, rather because of the complication that it introduces. Antibody immunity is a vital factor in protection against infectious disease and in overcoming actual bacterial infection. In the nonspecific reaction the therapeutic benefit, however, seems largely independent of the specific antigen-antibody balance. The fact that we do not discuss the antibody theory in this connection should not give the impression that it is to be ignored as a factor of defense and of resistance.

**Intoxication by Protein Split Products.**—Antibody resistance has been studied most completely in connection with the neutralization of the specific soluble toxins that are secreted by certain bacteria, notably the diphtheria bacillus, tetanus bacillus, etc. But we are beginning to take greater cognizance of the fact that in dealing with bacterial intoxication we have to do with other and less clearly defined toxic substances, broadly termed endotoxins to designate the fact that they form an integral part of the bacterial body. Some of these are possibly native proteins to which the infected organism can become sensitized, while others may be primarily toxic to the infected organism without previous sensitization. We must also consider: (a) *Preformed* protein split products which are toxic. This toxicity may be due to particular molecular grouping as the native protein molecule is broken up in the normal metabolism of the bacterial cell or to the chemical configuration of the fragments; those containing the benzol ring with its various addition radicals being most toxic (Baehr and Pick). (b) Protein split products *formed as the bacterial protein is fragmented in the host*—after the bacterial cell has died, i.e., not necessarily preformed in the bacterium. (c) *Toxic growth products* derived from the bacterial metabolism and excreted. (d) *Toxic metabolic products* derived from the *pathologic cellular metabolism of the invaded organism* (Jobling and Petersen, Zimmermann, etc.). In all these enumerated sources of toxic material derived either from the

bacterial cell and its metabolites or possibly from the pathologically altered activity of cells of the invaded body, proteins and their split products are the chief components with which we have to deal.\* Schittenhelm has emphasized the general conception that the splitting of proteins (apart from the gastro-intestinal processes) is purely an intracellular phenomenon and that whenever we have to do with extracellular proteolysis we deal with a pathological condition with tremendous inherent possibilities of intoxication. It is therefore our chief concern to investigate and review our present knowledge of protein intoxication, of enzymatic detoxication of the poisonous proteins, of resistance to protein intoxication and of the bearing of this knowledge to the problem of nonspecificity.

**Detoxication.**—It is apparent that the fundamental factor in overcoming bacterial intoxication (not due to the soluble exotoxins) lies in the ability of the cells or fluids of the invaded organism to digest the toxic protein fragments (and the native protein to which the organism may have become sensitized) to the lowest degradation product—that is, to the nontoxic stage, and in this way overcome the deleterious effect. This detoxication may also be brought about by the formation of addition products, by polymerization and by proteosynthesis in general. Enzyme activity, then, no matter under what immunological term we wish to classify the particular phase, must be considered among the basic phenomena which have to do with overcoming bacterial invasion itself. The study of the proteolytic enzymes and their relation to pathological conditions, of the factors that accelerate and the factors that retard enzyme activity should lead us to some final field wherein by controlling enzyme activity we may be able to achieve therapeutic results.

The rôle of the enzymes in pathological conditions has until very recent years been a relatively neglected field of study. Enzymes, whatever may be their nature or their composition, must have formed the basis of the structure upon which the animal organism built up its system of immunity. The unicellular organism must certainly endeavor to overcome harmful extracellular forces by means of its ability to excrete enzymes, and the intracellular enzymes, too, must be called into play when some parasite invades the cell. The path-finding work of Metchnikoff was based on this idea. Specific immunity must have been a much later development of this primitive and nonspecific factor of resistance. A number of investigators have at various times sought to identify the specific activity of antibodies, more especially the activity of complement, with various

\* While this view of the subject is plausible and quite generally accepted we must by no means ignore the fact that even here contradictory evidence has accumulated, a discussion of which will be found in the recent papers of Zinsser and of Tiele. These observers seek to find the source of the intoxication due to the "endotoxin" producing bacteria, as well as the intoxication in anaphylaxis, in certain physical alterations of the serum, as yet not clearly defined.

known enzymes, but without apparent success. The most recent work that has aroused the interest of the medical profession in this connection has been that concerned with the so-called Abderhalden reaction.

Abderhalden sought to show that whenever a specific protein was introduced parenterally into the blood stream, specific enzymes were mobilized which digested the protein so injected. This reaction of the enzyme and the substrate was demonstrated by means of the dialysis reaction. Unfortunately for this work the center of interest was early shifted from a study of the fundamental phenomena to particularistic and technical disputation of details involved in the clinical popularization of the test. Abderhalden was undoubtedly prejudiced in favor of the idea of the specificity of proteolytic enzymes because of his study and his familiarity with the beautiful specificity displayed by the enzymes that hydrolyze the carbohydrates. However, when one considers that the variety of carbohydrates with which the organism has to deal is relatively limited as contrasted with the endless combinations possible in the protein molecule, this prejudice is not necessarily logical. Possibly Abderhalden was influenced, too, by the immunological conception of specificity; indeed he seems to have had the hope that just this problem would find its solution in the specific proteases. The proof, however, that the Abderhalden reaction itself did not have the merit of strict specificity that its originator claimed for it (Plaut, Peiper, Jobling and Petersen, etc.), carried with it the tendency of checking further investigation in this field.

In this country a number of workers became interested in enzyme activity in relation to pathological conditions. Among these may be mentioned Opie and his associates and Jobling and his coworkers. Their papers have appeared chiefly in the *Journal of Experimental Medicine* during the years 1910 to 1917.

Buchner, Matthes and Krehl, Schmidt-Muhlheim, Schittenhelm, Fano, De Waele, Beidl and Kraus, Weichardt, Vaughan, Friedberger, Pfeiffer and numerous other investigators have established the causal relation between intoxication and fever and the protein split products. We therefore assume that with bacterial invasion the intoxication of the organism is due very largely to proteins and their split products derived from the bacteria. We must also deal with toxic protein material that is derived from the pathological tissues of the patient and perhaps from alterations in the colloidal state of the blood plasma that take place under certain conditions. For the moment the source of the proteins need not concern us.

If we are justified in ascribing major importance to the protein derivatives, we are assuredly justified in studying the mechanism of detoxication which must primarily involve the rôle of the proteolytic ferments that will break down the toxic complexes to nontoxic forms.

**The Serum Enzymes.**—In the blood stream several proteolytic enzymes are known to occur. These include the *leukoproteases*: (a) one that acts in a slightly alkaline or neutral reaction and is capable of splitting native proteins largely to the proteose stage; (b) one that acts in a reaction slightly acid, with a digestive range similar to the first; (c) an erepsin-like enzyme active in a neutral medium and freely hydrolyzing proteins from the intermediate stages (albumoses and peptones) to the amino acid forms. These enzymes seem to be derived from disintegrating but not from living polymorphonuclear leukocytes and fluctuations in the peripheral leukocyte count are not indicative of the relative titer of the enzyme concentration. (Hedin, Jobling and Petersen, etc.)

Apart from the leukocytes as sources of proteolytic enzymes we must consider those derived from the gastro-intestinal tract, the large abdominal organs and from areas pathologically altered, either by infection or by trauma, burns, toxins, etc. These enzymes include a *tryptase or protease*—a polyvalent trypsin-like ferment active in a neutral or slightly alkaline reaction. In the human this enzyme is normally present in only a very slight amount, but under certain conditions (pneumonia, leukemia) may be markedly increased. In certain animals one can also increase the amount by moderate stimulation of the liver (by Roentgen irradiation, etc.). In many of the smaller laboratory animals these enzymes are present in a considerable amount in the serum, especially in those that have no leukoprotease present in the leukocytes (guinea pigs, rabbits, etc.).

Serum *ereptase or peptidase* is an enzyme able to digest partly hydrolyzed proteins to the amino acid stage. It is normally present in human serum in small amount. But after feeding it is increased, probably entering the blood stream from the gastro-intestinal tract via the lymph current. It can also be augmented by stimulating the gastro-intestinal tract by means of short Roentgen ray exposure. In smaller animals this enzyme is present in relatively large amounts.

We have to deal in general with two types of proteolytic enzymes, (a) the true proteases capable of digesting the native proteins, and (b) the erepsin-like enzymes (peptidases) that are able to digest only partly hydrolyzed proteins; both active in neutral or at the most in a reaction varying from the neutral to only a slight extent. The enzymes of the first variety are, however, not active under normal conditions in the blood serum because their activity is inhibited or checked by the antiferment of the serum. In small localized areas the amount of true protease liberated by disintegrating leukocytes or by other causes may be sufficient to saturate the antiferment and in this case digestion may go the entire stage from native protein to amino-acids. As a general rule the protease derived from the leukocytes, active in the slightly acid reaction, is more active than the alkaline acting protease and autolysis therefore goes on much more

rapidly when the hydroxyl-hydrogen ion balance veers to the acid side. The increasing acidity acts, too, in hastening autolysis in another way in that the antiferment property of the serum is diminished as the acidity is increased. Both factors enter into the speeding up of enzymatic process when the reaction becomes slightly acid.

These proteolytic enzymes of the serum must not be confused with serum complement or alexin, as is frequently the case in immunological literature. In the antibody lysis of bacteria Jobling and Petersen showed that there was no associated proteolysis. Whatever type of enzyme activity may be involved in bacteriolysis, primarily it is not associated with proteolytic digestion. The evidence, uncertain though it is, rather indicates that the lipolytic enzymes are more closely concerned in this type of reaction.

Inasmuch as the true proteases of the serum are present only in relatively small amounts under normal conditions and are active only under special conditions (the decrease of the inhibitory factors) and then only locally, it is evident that the ereptases may assume greater interest.

The ereptase is potentially a detoxicating agent. Bearing in mind the fact that the toxic proteins are proteins that are already partially hydrolyzed or conjugated proteins dissociated from their non-protein radical, an enzyme that will attack these partially hydrolyzed proteins (albumoses [proteoses], peptones, etc.) and hydrolyze them to the amino-acid stage must necessarily be an agent of detoxication. A mobilization of this enzyme could then be considered only as of beneficial significance, never as a factor in the production of an intoxication, although the enzyme may appear accompanying intoxications. A spontaneous increase in the amount of this enzyme during the course of disease should therefore be coincident with clinical improvement, and conversely, the diminution of the enzyme should permit the accumulation of toxic split products and an increase in intoxication. It may be permissible to digress for a moment in order to study this condition in greater detail and examine the relations as they are presented to us in lobar pneumonia.

**Pneumonia.**—For a number of years investigators have emphasized the possibility that a definite relation exists between the inception of the crisis and the activation of the proteolytic ferments in the area involved. Edsall and Pemberton in particular advanced this idea and endeavored to make the logical clinical application of hastening autolysis as a therapeutic measure in cases of delayed resolution. Later Jobling and his associates studied the serum ferment and antiferment during the course of lobar pneumonia, noting that just preceding the crisis protease was demonstrable in the serum while the antiferment began to diminish from the high titer prevalent throughout the early part of the disease. The work of Weiss on the crisis is similar in character and sets forth analogous conclusions. Lord and Nye have

approached the same problem and lay stress on the changes that occur in the hydrogen ion concentration of the exudate of the pneumonic lung, which, on being increased, makes possible a suitable reaction for the augmented activity of the proteolytic enzymes. Abderhalden in investigating the enzyme activity of pneumonic sputum before and after the crisis was not able to determine the presence of any peptidase before the crisis, but with the inception of the crisis found such enzymes present in large amounts. The fundamental idea underlying the studies in this direction has been that apart from the intoxication arising directly from and incident to the growth of the pneumococcus, toxic split products were absorbed from the exudate, which indeed could be considered a mass of foreign protein undergoing slow digestion before the crisis. Active autolysis once under way, only the lower and nontoxic split products would be absorbed and the environments for the further proliferation of the pneumococcus would become unfavorable, for, as Almaggia has shown, pneumococci are very susceptible to products of autolysis. In this phenomenon the reaction is primarily a local and a cellular one, involving the liberation of sufficient leukoprotease from the disintegrating leukocytes and the gradual alteration in the reaction of the medium so that the inhibitory factors—i.e., the alkalinity and the excessive amount of antiferment—are overcome. Of the varieties of the proteolytic enzymes entering into this reaction, Jobling and his associates studied in particular the protease, as before mentioned, while Petersen and Short studied the ereptase titer.

We can assume that this latter form of enzyme activity would be of favorable import in the process inasmuch as it could lead only to detoxication through the complete destruction of toxic protein fragments. The first two charts illustrate common clinical pictures in lobar pneumonia, the one recovering by lysis, the other terminating fatally on the ninth day of the disease.

Case No. 1. White man, 43 years of age, entered hospital March 14, 1917, after an illness of 36 hours. Diagnosis: Lobar pneumonia of lower right lobe; course uneventful, recovery by lysis by the tenth day. (See Fig. 4.)

It will be observed that the ereptase titer (peptidase) remained uniformly low during the first three days when examined, then increased to approximately 3 times the former titer on the 8th day of the illness and then again diminished. The increase coincides with the period of clinical recovery. The antiferment titer shows the usual increase early in the disease and a diminution during the period of lysis that is frequently observed.

Case No. 2. Colored man, 27 years of age, entered the hospital April 18, 1917, having been ill for two days. Diagnosis: Lobar pneumonia of the lower left lobe; aortic regurgitation. On the third day there were evidences

of the involvement of the right lobe as well, and the patient became progressively worse, death taking place on the ninth day of illness.

It will be noted in Figure 5 that the titer of the ereptase is in this case the reverse of the previous one, a decrease, being appar-

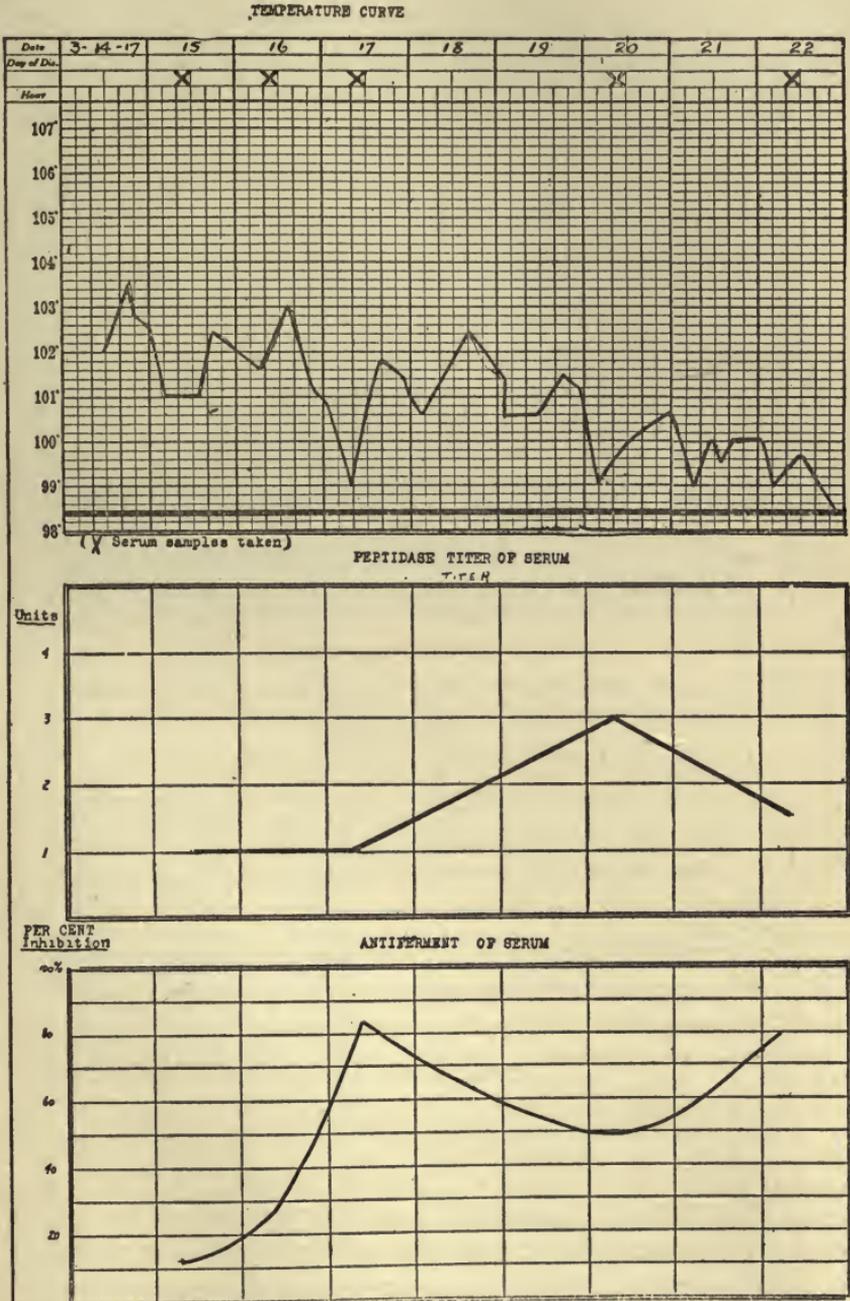


FIG. 4.—The ereptase (peptidase) and antiferment titer during the period of lysis in pneumonia.

ent after the 3rd day that persisted until death. The antiferment during this time progressively increased. This reaction curve of the enzymes is characteristic for fatal pneumonias.

The case illustrated by Figure 6 is perhaps the most interesting in illustrating the relation of the ereptase titer to the clinical condition of the patient.

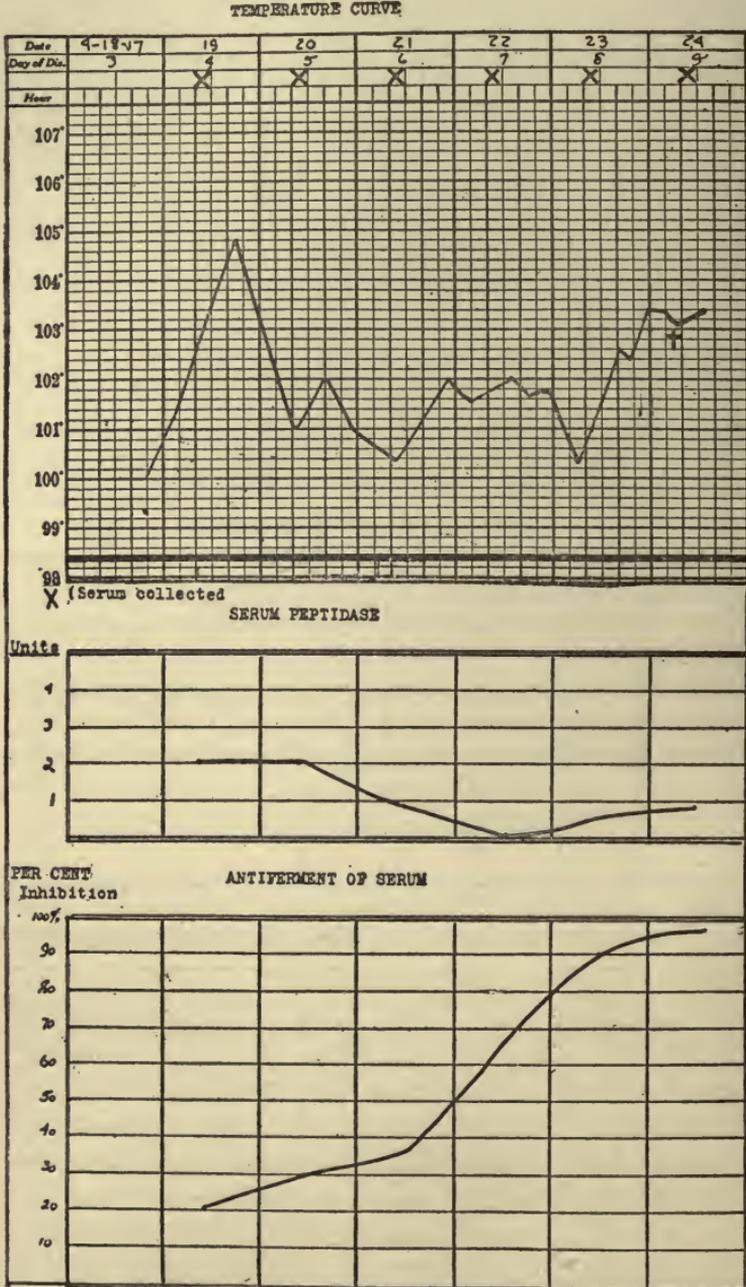


FIG. 5.—The ereptase titer and antiferment in pneumonia terminating in death.

Case No. 3. White man, age 34 years, entered the hospital on March 5, 1917, with a diagnosis of lobar pneumonia of the lower right lobe of three days' standing. The course of the disease was quite protracted. By the 4th day after admission the temperature had declined and the patient

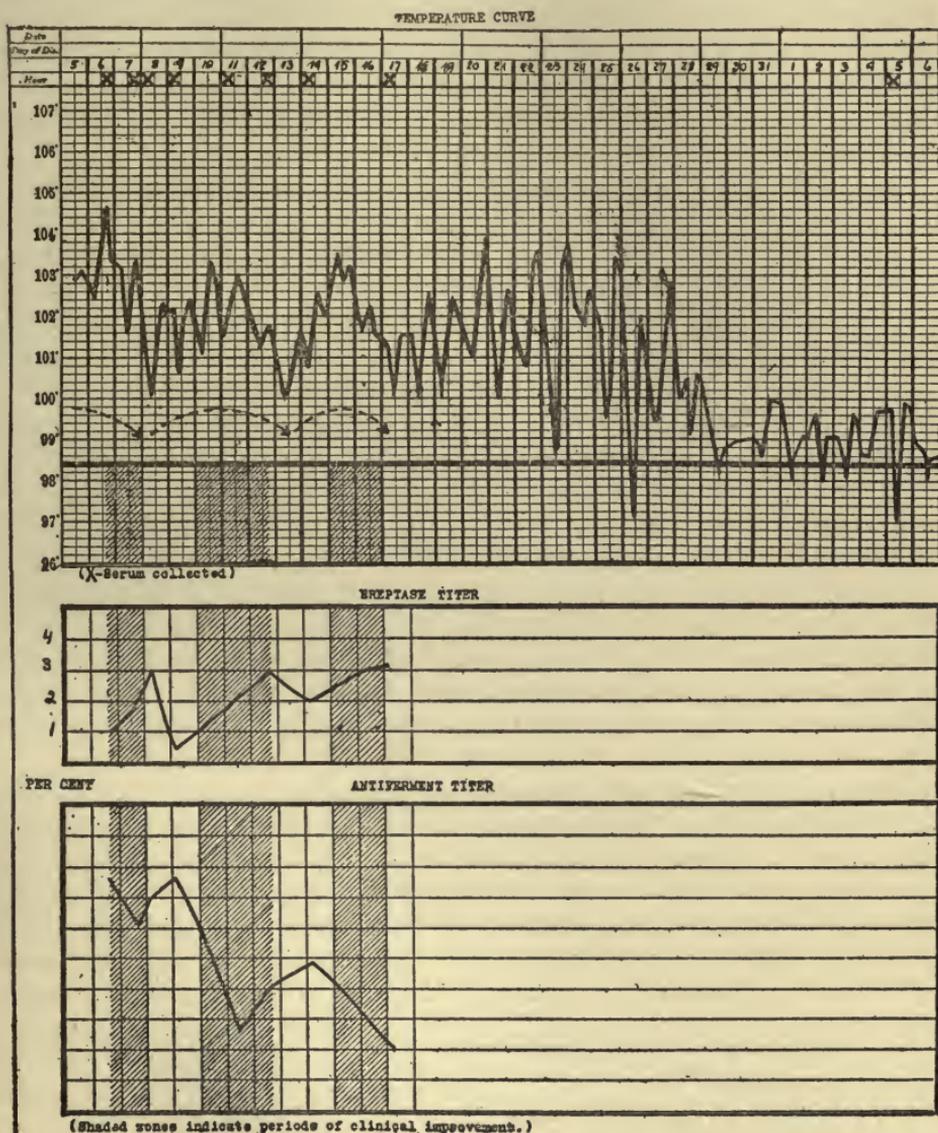


FIG. 6.—The relation of the clinical condition during pneumonia to the serum breptase and antiferment.

was clinically improved when an extension to the middle lobe occurred. The temperature increased for several days, then declined to the 8th day. At about this time the lower left lobe became involved, which entailed another rise in temperature, followed by a period of partial recovery with a long period of violent temperature fluctuations superseding. A month after admission the patient was still running an irregular febrile course

although greatly improved clinically. At this time a final blood examination was made.

We have in Figure 6 shaded the portions when the patient was making clinical improvement after each lobe was involved. The evidences of clinical improvement—pulse, respiration, subjective symptoms and physical findings—coincided with typical changes in the enzyme concentration of the serum as can be observed from the chart.

An increase in the ereptase titer took place during each period of improvement studied (the time blood samples were drawn is indicated on the chart by X) but declined when the clinical condition was unfavorable. The antiferment on the other hand invariably tended to diminish during the favorable periods and to increase with the increase in the lung involvement. These alterations are so typical and so clear cut that their clinical significance cannot well be questioned, even though the interpretation of the changes may be open to discussion.

In the pneumonia that terminates by crisis or by lysis an increase in the ereptase titer was invariably observed by us either preceding or accompanying the clinical change. In cases that terminated unfavorably such an increase was not found, the titer in these cases usually remaining below that observed in normal individuals. The antiferment titer of course does not directly influence the activity of the ereptase, nevertheless as the patient improves the antiferment diminishes. The entire condition is one therefore that favors a rapid digestion of proteins.

**Ferment-Antiferment Balance.**—When we now come back to our consideration of the true proteases we deal with a reaction which is much more complex in its character and its possibilities for two reasons: (a) The enzyme action may involve the splitting of native proteins to the higher split products. If this concerns a nontoxic native protein to which the body is not sensitized it implies that a new toxic substance is produced in the organism itself. If on the other hand it involves a toxic protein or one to which the organism has become sensitized, then the enzyme can act, too, as a detoxicating agent when it splits the protein. (b) The ferment action is balanced by an antiferment and we have therefore to deal with two variable factors.

For purposes of illustration the pneumonic condition will again serve. Let us assume that the pneumonic focus with its mass of cellular detritus represents, for the normal tissue, simply so much foreign material from which it must free itself by digestion. As long as digestion proceeds slowly, higher and more toxic split products will be absorbed as such; digestion proceeds slowly because the leucocytes are still living (therefore not shedding their ferment), because of the alkalinity of the reaction of the exudate, and the large

amount of antiferment present in the exudate which, of course, inhibits digestion. If now the antiferment is lowered, either because of the change in the reaction or because it is saturated by protease mobilized from some other organ, while at the same time protease and ereptase are liberated locally, the patient will be detoxicated promptly as digestion changes from a state of inhibition to one of acceleration. In this case the liberation of the true protease would be associated with detoxication.

Let us assume on the other hand that we are dealing with a quiescent tubercle, one that is sufficiently protected by a connective tissue encapsulation to prevent the absorption of toxic material from the focus that has been walled off. If for any reason the identical serum reaction or local reaction that has been hypotheticated above should occur in such a patient quite the opposite clinical effect would ensue. The liberation of protease would, along with the reduction of the antiferment (protective) titer, promptly begin to digest away the connective tissue of the capsule and allow some of the toxic material from the focus and the native proteins of the focus as well, to escape into the general circulation with a resulting intoxication of the patient and activation of the focus. Fluctuation of the protease titer can therefore be assumed to influence pathological processes in a fundamental way and at times with diametrically opposite clinical results. But this fluctuation of the protease is under the control to a certain extent of the antiferment or inhibitory substance, which thereby becomes an integral part of the balance which we have under consideration. Here we leave the enzymes and have to deal very probably with lipid substances. The antiferment is not an antibody in the immunological sense, although it was early so considered; it consists of the highly dispersed unsaturated lipoids of the serum and of the lymph and the tissues.\* Its titer varies therefore with at least three conditions: (1) the amount of the lipoids present, (2) the dispersion of the lipoids, (3) and the chemical structure, that is, the degree of unsaturation. All these conditions are subject to considerable variation and any of them may cause a change in the titer.

Thus changing of the dispersion by acidifying, by salting and by heating to a sufficient degree inactivate the antiferment, physical adsorption by certain chemically inert adsorbing surfaces such as fuller's earth, barium sulphate, agar, etc., lowers the titer; solution of the lipoids by chloroform, ether, acetone, and certain of the alcohols removes the antiferment from the serum. The soaps of the unsaturated fatty acids are perhaps the most comparable substances which are available and with them one can simulate many of the

\*The evidence concerning the nature of the antiferment is conflicting. Bach and Teale were not able to confirm the results of Jobling and Petersen. The papers of Tachigara, Fujimoto, etc., should be consulted.

reactions that can be obtained with the serum antiferment. There is much evidence that the antiferment lipoids are in more or less close physical combination with the serum albumin. With this fraction they are thrown out of solution with the usual methods of separating the serum proteins.

Clinically it is known that the antiferment is augmented during a number of conditions, notably in the acute infections, in pregnancy, in carcinoma and cachectic states in general; following anaphylactic and other shock reactions, including therapeutic vaccination, and in certain pathologic processes of the central nervous system characterized by degenerative changes. In other words, the increase in antiferment is part and parcel of a general reaction phenomenon of the body. This increase seems purposeful in that an increase in the antiferment titer would tend to counteract the negative nitrogen balance incident to the heightened destruction of proteins of the body commonly observed in toxic conditions.

This relation of the antiferment to the rate of protein metabolism has been worked out in rabbits and dogs during inanition by Jobling and Petersen. They found that the excretion of nitrogen in the starving animal was in inverse proportion to the amount of antiferment in the serum, as will be apparent from the following table:

Animal No.	% Inhibition (Average for 5 Days)	Nitrogen Excreted (Total for 5 Days)
1	41%	4.24 gms.
2	66%	2.95 gms.
3	71%	1.97 gms.
4	73%	1.99 gms.

This holds true evidently for the human, although it has not yet been fully worked out in normal individuals. Wilson, for instance, noted the increased storage of nitrogen during pregnancy, a condition associated with a well-marked increase in the antiferment titer. After vaccine shock or protein shock we often find the same increase in weight during the time when the antiferment titer is increased. Thus Holler injected himself over a period of two weeks with daily intravenous doses of 1 c.c. of deuteroalbumose solution (10%); there was no clinical reaction corresponding to that observed in patients ill from any disease. The chill, sweating and temperature were all absent but he gained in weight during the course of the injections. This has been the general experience of the clinic as well as the laboratory.

If we keep these simple enzyme balances in mind, many of the changes which are encountered following nonspecific therapeutic injections will appear quite simple and logical. One balance consists of (a) the true proteases capable of splitting native proteins all the

way to their lowest split products. These can act, therefore, either as (1) intoxicating agents when splitting nontoxic native proteins to the toxic stage, (2) or as detoxicating agents when free to split the partial products of digestion to the nontoxic forms or when splitting a native protein to which the body has become sensitized. These enzymes are counterbalanced by (b) the antiferment of the serum, a variable factor. The ereptase (c) or peptolytic enzyme, capable of splitting only the partly hydrolyzed proteins (toxic) to the amino acid stage (nontoxic) and therefore to be regarded as a detoxicating agent, not counterbalanced by an antienzyme and therefore free to act whenever present in the serum and the tissues.

This conception of a balance of variable factors which at one time may act in a detoxicating manner, and in other cases may intensify a disease process, has been discussed fully in several papers and we need go no further into the details at this time. (Jobling and Petersen, Jobling, Eggstein and Petersen, and Petersen.)

**Nonspecific Injections in Carcinoma.**—Von den Velden, who was one of the very first to use nonspecific methods in the treatment of disease (1906), early expressed the hypothesis of enzyme action as the basis of the therapeutic results and has maintained this ever since. He began his work using small subcutaneous doses of serum albumin and ovalbumin in 5 and 10% solution. From these he passed to the use of convalescent serum, tetanus antitoxin, normal horse serum, and finally to the use of milk injected intramuscularly. In treating several cases of inoperable carcinomata he observed that following the injection the patient reacted with a period of malaise and of fever for a period of several days and then for a time the general condition of the patient improved. There were a gain in weight, a better appetite, lessened pain, etc. Under the treatment the tumor would, at times, show decided regressive changes. With tuberculin injections Dabney observed a similar effect.

This experience of von den Velden is cited in this connection merely because it is typical of the result achieved by all the nonspecific agents in the treatment of carcinomata and other malignant diseases. Beard got the same result when he injected trypsin; Coley's fluid and tumor autolysates give a similar reaction; colloidal metals give it. The mechanism is the same in all cases, the clinical picture is identical, the results are similar, i.e., there are evidences of a decided focal reaction, even of tumor regression in size, but the actual proliferation of the neoplasm is not checked because the vascularized portions of the tumor are in nowise interfered with, the regression being due to an increase in the necrosis of the central and less vascularized portion of the neoplasm.

Let us assume that an injection of milk has been made intramuscularly in such a carcinoma case. The temperature heretofore has been practically normal. Several hours after the injection there

may be a chill, the temperature rises sharply and instead of dropping after a few hours, as it would in an ordinary infectious case, stays high for from 24 to 48 hours. Usually this reaction is accompanied by general malaise and every indication of increased inflammatory reaction about the tumor. After this period the temperature drops, the patient feels better than before the injection, gains in weight, pain is lessened and retrogressive changes are noted in the tumor. It has been shown that following such an injection of a nonspecific agent a definite shifting of the ferment-antiferment balance takes place so that the antiferment is lessened and the activity of the protease increased. At the tumor site this means that this protease begins to digest some of the native proteins of the necrotic débris. Toxic split products are liberated, they diffuse out from the focus into the surrounding healthy tissue, cause irritation, the attraction of leukocytes, vascular engorgement, increased tension and with it increased pain. It is during this period of absorption of the soluble split products that the febrile period and systemic effect of a general malaise are observed. The leukocytes attracted by the digestive inflammatory reaction partly succumb, partly migrate from the field. A certain amount of leukoprotease is certainly liberated from them. During this period, too, we have an increase in the amount of nitrogen excreted—i.e., a negative balance. Then follows the period of recovery of the balance and the change to the reparative side. The antiferment is increased over the amount present before the injection; the protease action is checked, increased amounts of ereptase make their appearance and detoxicate whatever remnants of split products still remain near the focus. During this period the patient manifests every sign of clinical improvement—euphoria, increase of weight, appetite, etc. The increase of weight that follows the increase in the antiferment curve has been worked out in a series of clinical conditions by Breed.

The tumor in the meantime may have actually decreased in size by the effects of the reaction because a certain amount of necrotic material has been digested away. It is of course evident that the living tumor cells need in no way be susceptible to the effect of the enzymes and that the reaction, as far as a matter of cure is concerned, is not to be regarded as a therapeutic agent for such malignant conditions. It may have a place in the therapy of malignant conditions if by producing an inflammatory reaction repeatedly we can, either by cellular or vascular changes, aid in the resistance of the body to the neoplastic invasion (Theilhaber). Until we have certain knowledge of these factors in tumor growth we must unfortunately deal more or less empirically with the conditions. Nor must it be forgotten that the inflammatory reaction that is brought about may at times not be helpful but may actually stimulate the tumor cells to greater activity and malignancy, and therefore be of

decided harm to the patient. If, however, it is clearly kept in mind that only clinical improvement and amelioration is sought and the measures used in this sense, then it may have a place in our legitimate methods of treatment in inoperable cases.

This reaction and its effects on the local condition as detailed here is quite similar to that which has been studied in regard to the tuberculous focus and is more fully entered into elsewhere.

**The Reaction in Local Inflammation.**—It is of paramount importance for the purpose of studying the rôle of the enzymes in this non-specific reaction to keep in mind the fact already emphasized in the introduction that the reaction of the body to injury, whether chemical or physical or bacterial, is, within certain limits, always the same. Inflammation, no matter how produced, is fundamentally alike in character and in its results.

If we view recovery from this point of view it is instantly apparent that nonspecific therapy offers something more substantial than an evanescent therapeutic fad or a bizarre fancy of the day in medicine. It is rather a procedure that has as the foundation of its mechanism biologic processes at once the most primitive and the most universal of all those over which the organism disposes in its measures of defense and resistance to trauma and disease.

If it can actually be demonstrated that inflammation is altered by nonspecific reactions we can conceive that the hastening of the process will be evidenced in two ways: in one, that a beginning inflammatory process will subside without suppuration, in the other, that an advanced or rapidly advancing inflammatory process will undergo softening and resolution. As a matter of fact these are precisely the reactions that do take place when we treat local inflammatory processes by nonspecific means, the venereal bubo being a condition of this type that has been extensively studied. (Odstreil, Müller, Schneller, Antoni, etc.)

When a bubo is treated by the intragluteal injection of milk one can observe a definite focal reaction which reaches its maximum in from six to eight hours with an increase of pain, local tenderness and hyperemia. Following this a period of analgesia sets in. If such a bubo is taken under treatment early, suppuration never takes place, the process subsiding without it.

If the local inflammation, on the other hand, is further advanced when treatment is commenced, softening occurs soon after the injection, but if further injections are then made no incision or drainage is necessary, according to Müller, because the necrotic and softened material is rapidly absorbed. In only one out of 25 cases did Müller find it necessary to drain the bubo.

This effect on local inflammatory processes, which has been discussed at greater length in the chapter on The Focal Reaction, can be demonstrated after nonspecific injections wherever the lesion is so

located that it can be observed directly, as in the skin or mucous membranes. In the deeper tissue it is made clinically evident by the invariable symptomatology that follows the injections—first an increase in the evidence of pain and temperature, later a complete subsidence, either transient or permanent as the case may be.

We believe that the explanation for these phenomena is relatively a simple one, although it involves at some time practically all of the tissues and structures about the focus of inflammation, changes in both the blood and lymph vessels and nerves, as well as in the local tissues directly involved.

With the injection there is first apparent an increased excitability of the central nervous system and the sympathetic system; later this subsides and ends in a period of lowered excitability. There is at first apparently a direct effect on the capillaries so that they become more permeable—the lymph flow is increased, the tension of the local inflammatory focus is greater—the pain augmented. Later the reverse sets in and the capillaries become less permeable.

But in the meantime certain alterations have occurred in and about the focus. We may assume for the purposes of illustration that we are dealing with this early bubo—a certain amount of toxic material (protein split products from the necrotic tissue of the venereal focus, bacterial endotoxins, perhaps soluble toxic materials from bacteria, perhaps a few bacteria themselves have filtered in along the lymph channels) has been brought to the gland and has incited an inflammatory reaction. This finds its expression in the hyperplasia of the endothelial cells of the lymph channels, in an attraction of polymorphonuclear leukocytes and the exudation of fluids into the tissues. As yet there has been no necrosis.

The tissue fluids bathing these cells contain little protease or ereptase but much antiprotease (antitrypsin) so that digestive processes are held in abeyance. Under ordinary conditions the intensity of the intoxication is therefore not diminished and tissue necrosis finally results, both the fixed cells and some of the polymorphonuclear leukocytes being affected. From the latter we now have the liberation of a considerable amount of protease, sufficient to saturate and thereby negate the effect of the antiferment in a circumscribed area—digestion begins to take place—solution of tissue and fluctuation.

If on the other hand at an early stage the patient is given a nonspecific injection the focus is very promptly flooded—the lymph flow as measured in the thoracic duct is increased fourfold—and in the fluids now exuded (the permeability of the capillaries being increased by the nonspecific injection) there is carried considerably more protease as well as ereptase, while the antiferment is diminished. The toxins present are not only diluted but their digestion is commenced by the enzymes. Necrosis is prevented by this effect on the toxins. The capillaries now become less permeable, the fluids

are diminished, tension and pain lessened and restitution to the normal takes place.

On the other hand we may suppose that the process had already proceeded to the stage of actual destruction of some cellular elements. We bring about the nonspecific reaction at this period. Here the flooding of the area with exudate, the lowering of the antiferment, the increase in the proteolytic enzymes will of course accelerate the autolytic processes already commenced. But this digestion will coincidentally tend to diminish the acute toxic effect of the split products and other toxic protein material that originally caused the inflammation; solution of the necrotic focus with subsidence of the acutely inflammatory phase of the reaction will result and the further treatment by nonspecific injections will merely aid in the absorption of this soluble material from the focus. It becomes clearly evident therefore that the identical reaction may alter an inflammatory focus in seemingly diametrically opposite ways—restitution without suppuration, as well as the acceleration of suppuration with absorption following.

**The Reaction in Inflammation of Nonbacterial Origin.**—Nor must it be presumed that this process as here depicted holds true merely for a bacterial process. A similar reaction takes place when we deal with gout and when we deal with a chemical injury such as that following a typical "war gas" effect, as for instance mustard gas. Von den Velden's observations will be of interest in this respect.

"I had considerable opportunity in the field to study the effect of nonspecific therapy in mustard gas poisoning, being led to try the method not only by the clinical observation but by the autopsy findings as they presented themselves to us. I need but briefly mention in this connection that the effects of the gas, as shown in the effects on the mucous membrane of the respiratory tract, varies from the mildest catarrhal inflammation to widespread and extensive croupous and finally ulcerative changes. In view of the oftentimes decidedly malignant and complicated course of the clinical picture, I endeavored to treat as early as possible the cases in which the toxic manifestations were most severe, or those in which the clinical picture was one becoming progressively worse from day to day, in order to avert the secondary pneumonias and the abscess formation and especially the ominous bronchial stenosis so common a sequel. From my previous experience with nonspecific therapy an early interference by means of an acceleration of the inflammatory processes might be expected to yield very gratifying clinical results. Of course, these might be of purely symptomatic nature.

"While my experience extended over a larger number, I have recorded observations on approximately 100 cases of gas poisoning treated either with horse serum (5-10 c.c. intravenously), milk (10-20 c.c. intramuscularly) and tetanus antitoxin (5-15 c.c. intrave-

nously) with from one to three injections. The cases included moderately severe incipient cases with severe hoarseness and beginning bronchial stenosis without secretion; severe cases with croupous inflammation extending from the pharynx deep into the bronchial tree, some of them already complicated by pneumonia; as well as older cases with severe bronchorrhea (with as much as 3 liters of secretion per day) with evident peribronchitis, pneumonia, abscesses and in some instances lung gangrene. It is natural that in these latter cases the injection had little or no effect and that the most satisfactory results were achieved in those of the first category. Inasmuch as a spontaneous recovery is, however, very common in this class of patients this result was to be expected. It was in the second class of patients, however, that the most convincing evidence as to the value of the injections—and this not only in my own estimation but in that of my attending colleagues as well—was forthcoming. In from 6 to 10 hours after the injection the first favorable results of the injection were to be noted, first in a diminution of the stenotic symptoms—lessening of the cyanosis, improvement of respiration, diminution of the cough and a freer secretion. Very instructive was the solution of a membrane that had been present in the pharynx of a patient and which could be observed readily. And to this local effect, which was of far-reaching therapeutic benefit in the further progress of the lung pathology, as well as indirectly on the circulation, there was added, sometimes only after two or more injections, a more or less pronounced critical drop in the temperature curve, an effect the origin of which one may explain in a variety of ways. I unfortunately have not been able to tabulate the results as compared to cases not treated with injections because of fortuitous circumstances.

“The success, which surely cannot be specific in any way, corresponds to experience gained with nonspecific injections in other diseases and the effect on the pathological process is similar:—a marked local effect on the more or less severely inflamed mucous membrane of the respiratory tract with an acceleration of the dissolution of membranes, a cleaning of ulcerative processes and perhaps an inhibition of inflammatory processes just beginning. The success was so frequent and apparent that chance was to be excluded.

“On the skin lesions the injections seemed to have no effect. With collargol intravenously injected, I gained the impression that effects similar, but not so striking, were to be obtained, and it may be of interest to note that Aschoff obtained comparable results in the treatment of gas poisoning by injecting diphtheria anti-toxin.”

**General Inflammations of Bacterial Origin.**—So much for the therapeutic effect to be observed on local pathological processes. When we deal with general infections we meet conditions less

simple and in which speculation and conjecture must enter to a larger extent. Perhaps it will be most satisfactory to discuss the status of our information in a definite variety of diseases, each differing in fundamental pathology, and each yielding different results when nonspecific therapy is used.

(A) In typhoid fever we deal with an infection originating with a gastro-intestinal infection followed by an infection chiefly of the lymphopietic system and a concurrent bacteriemia. Here the intoxication is principally due: (1) to native proteins derived from the typhoid bacillus and to which the organism has become sensitized during the incubation period of the disease, (2) to very toxic protein split products contained in the body of the bacterium (endotoxins), and (3) to split products from the bacterial cell when it undergoes proteolysis. The disease is one to which an active immunity can be established.

(B) In pneumonia, on the other hand, we are dealing with an infection differing from this materially. Leaving undetermined its method of invasion—whether primarily a blood invasion that localizes in the respiratory tract or an extension directly along the respiratory tract (which seems most probable), we deal with a localized inflammatory process, probably without sensitization of the body to the native protein of the pneumococcus, a process in which the toxic manifestations are due to an absorption of the higher split products derived from an inflammatory exudate (fibrin, cell detritus, etc.) located actually on the surface of the body (considering the pulmonary alveoli in their actual relation to the surface an invagination, not from their mere anatomical position as part of the internal organs). Because of the vascular supply the alveolar surface is naturally an ideal absorbing structure, so that, while largely isolated during the course of a lobar pneumonia from the general circulation, absorption is still sufficiently great to cause a profound intoxication. The pneumococcus protein itself is not particularly toxic and as already stated the organism not necessarily sensitized to it; the bulk of the toxic manifestations must come from the splitting of the exudate in the pulmonary alveoli. It will be recalled that Kaznelson found the split products obtained from fibrin particularly toxic. Here we deal with recovery frequently by crisis rather than by lysis and with an immunity of low grade and of relatively short duration.

(C) Finally we might take as an example a pure septicemia of the streptococcus type, without localization, where intoxication is associated with marked virulence on the part of the organism rather than by the production of a soluble toxin from the bacterium or a toxic autolytic product from tissues of the invaded host.

**Typhoid Fever.**—Our observations in typhoid fever are perhaps most complete and from them we may be able to construct a picture of the processes that follow the nonspecific reaction. Let us assume that

we have given a proteose injection to a typhoid patient during the first week of the illness. He has responded with the typical chill, a sweat, rise in temperature curve, and a leukocytosis. Following the reaction his temperature comes to normal and remains so, the patient feels well and as far as can be determined is clinically cured. In some 20-30% of typhoid patients injected we can observe precisely this result. What has cured the patient?

1. It has been stated that despite this clinical recovery typhoid bacilli may in some instances still be cultivated from the blood of the patient several days after the injection (Rohonyi). Decastello's work throws much doubt on this particular point.

2. The patient may still present rose spots, an enlarged spleen, a positive diazo reaction and a leukopenia (Lüdke); Holler in his series only noticed the occasional splenic tumor after the recovery.

3. Healing of typhoid ulcers takes place within a few days after the injection, as determined by autopsy in patients dying of inter-current disease, after recovery by means of nonspecific therapy (v. Wiesner).

4. Fluctuations in the antibody concentration of the serum do not account for the recovery. In some cases they are increased, in others actually diminished, despite comparable clinical results. Nor is the hypothesis valid that when diminished it affords evidence that the antibodies have been used up during the process of recovery. Recovery from typhoid takes place normally in leukemic patients who never produce antibodies (Moresci, Howell).

5. The cells of the organism are all stimulated (omnicellular plasmaactivation of Weichardt) when injected intravenously. The stimulation can be measured in the increased activity of the glandular parenchyma, in increased motility of smooth musculature, in the increased work capacity of the heart muscle.

6. The permeability of the cells is altered. Due to this effect and the coincident stimulation above mentioned, enzymes, fibrinogen, thrombokinase and glycogen are thrown into the circulation, and antibodies, if the organism has been previously sensitized, are also discharged from the cells and flood the blood stream.

7. The altered permeability of the cells finds further expression in the augmentation of the lymph flow, directly to be observed about an inflammatory focus or to be measured at the thoracic duct. It is also manifest when the permeability (to certain dyes) of the capillaries about an inflammatory focus is studied. The endothelium becomes at first more permeable, later less so.

8. This change in the permeability of the cell membrane whereby the exchange outward and inward is augmented must of course depend on actual changes in the physical structure of the lipoid-phase which probably forms the membrane of the cell.

9. This change in the membrane of the cell probably accounts

for the increased resistance to intoxication after the injection and forms part of the mechanism of antianaphylaxis. Whether an actual loss of lipoidal constituents of the cell membrane takes place which, when thrown into the circulation, then form part of the antiferment, is not determined.

10. An increase in the antiferment of the serum occurs after the injection and persists as a rule for some days.

11. The alteration in the cell membrane is evidenced furthermore by the change in the irritability of the central nervous system and in the sympathetic nervous system.

12. There is finally a mobilization of leukocytes due to a more or less specific stimulation of the bone marrow.

While all these changes are brought about there seemingly are two that are of vital importance—the stimulation of the cells—plasma stimulation of Weichardt—and the alteration of the permeability of the cellular membrane. All the others are of interest and very likely to take some part in the result, but all are more or less due to these two fundamental changes.

*There is an increased tolerance to intoxication.* The patient, despite the fact that he may still have a positive blood culture, no longer is sensitive to intoxication. The experimental basis for this clinical observation has been laid by Starkenstein who demonstrated that after a variety of nonspecific injections the organism becomes more resistant to intoxication, even to poisons such as phenol and strychnin. This is probably due to the decrease in the permeability of the cell membrane that follows on the initial increase in permeability.

*The toxic material is more rapidly destroyed.* Due to the cellular stimulation and the mobilization of the proteolytic enzymes, proteolysis is hastened. This affects (1) the native protein of the typhoid bacillus to which the body during the course of the incubation period has been sensitized and (2) the toxic split products derived from the bacillary disintegration (endotoxins) which are now split to their lowest stages and eliminated.

*The lymphagogue effect (increased permeability of the capillaries) floods the lymph spaces.* If we conceive of typhoid fever as a local disease and not a septicemia, the curative process must take place at the site of the lesion. It has been demonstrated that both in normal and immune animals the antibody concentration is greater in the plasma than in the lymph. The serum in typhoid fever is invariably rich in bacteriolytic substances, the transient and low-grade bacteriemia notwithstanding. With the active passage of antibody rich plasma into the lymph spaces the destruction of the typhoid bacilli will take place and healing will be explained. (This theory was put forward by Teague and McWilliams.)

*The increase in the anti-enzyme in the lymph spaces makes the*

*further proliferation of the bacteria difficult.* Bacteria must obtain their nitrogen from the lowest degradation products of proteins; they cannot use peptones and proteoses and the higher split products. When the antitrypsin is increased their extracellular protease is inactivated and their metabolism interfered with (Wright).

On this basis we have observations that account not only for the detoxication of the patient, which is commonly observed after non-specific protein injections (the euphoria being a constantly reiterated clinical observation) but for the actual destruction of the bacteria and the checking of their further proliferation.

Into this mechanism other factors may and possibly do enter. Thus the question of the effect of the leukocytosis has repeatedly been raised. The intravenous injection almost invariably results in a marked augmentation of the peripheral leukocyte count, following the initial leukopenia. This has been considered as the possible mechanism involved in the recovery. But it has been observed that recovery may take place without the appearance of this leukocytosis. Inasmuch as the blood serum itself is able to destroy the bacilli without the intervention of leukocytes, their usefulness in this connection is not of paramount interest. As a matter of fact Rous has shown that the typhoid bacilli may be protected from the effects of serum lysis after they are ingested by the endothelial leukocytes. It is much more probable that the rôle of the leukocyte lies in its detoxication of the bacillary proteins of typhoid bacilli already dead when ingested, or so altered by serum contact that the leukocyte can finally destroy them after ingestion. Of course the concentration of the leukocytes in the internal organs—spleen, liver, lymph glands, intestinal tract, lungs, etc.—immediately after the injection (during the time of the peripheral leukopenia) at the very site of the chief local foci of the typhoid proliferation may lend particular importance to the leukocytic reaction in typhoid fever.

**Lobar Pneumonia.**—Let us turn to examine the effects of non-specific therapy in lobar pneumonia. Blake and Russell have in recent papers thrown considerable light on the questions involved in the mode of infection in lobar pneumonia and their observations confirm the clinical impression prevalent for a considerable period that true lobar pneumonia takes place by extension of infection along the trachea. According to their study the pneumococcus invades the lung tissue at some point or points near the root of the lung, spreading subsequently throughout the lobe by way of the interstitial framework and the lymphatic system. It is therefore to be regarded primarily as an interstitial infection of the lung. Rosenow, among others, as a result of blood culture work had endeavored to place pneumonia among those diseases that are primarily a septicemia and later become localized in some tissue of predilection. But Blake and Russell found that the blood became infected from the bacteria having

gained access to the blood stream from the lymphatics and that this bacteriemia took place quite early, even before the onset of clinically localizing symptoms.

Pneumonia must be regarded, therefore, as a directly localized disease and not primarily as a septicemia.

It is the critical termination of the disease that has always interested physicians and a number of ingenious theories have been elaborated to account for the process. But as long as we sought the solution of the problem along strictly immunological lines none of the hypotheses put forward seemed sufficient to account for all the phenomena observed. At times antibody concentration was altered before or during the crisis, at other times no alteration could be demonstrated.

In more recent studies a different line of thought has been followed, and it has been made probable that we must seek part of the explanation in purely physicochemical alterations that seem operative in the mechanism of the crisis. Müller some years ago emphasized the importance of the proteolytic enzymes of the involved lung area in bringing about resolution. Later Jobling, Petersen and Eggstein advanced the hypothesis that the intoxication in pneumonia was of dual origin, from the invading organisms and also from the autolytic products of the involved tissue and exudate. Weiss, Lord and Nye have developed this same thought. According to this conception recovery in pneumonia is associated with the inauguration of active proteolysis of the pneumonic exudate, brought about, according to Lord, by an increase in the local acidity to such a degree that the autolytic enzymes find a suitable medium for activity; according to our conception, by an increase in the amount of autolytic enzyme either from destroyed leukocytes (leukoprotease) or from mobilized protease from distant organs, and associated with a decrease in the antienzyme (antitrypsin), by saturation with the excess of protease, by increase in acidity, or by the general lowering of the antitrypsin titer of the body. The whole phenomenon in its sharp demarcation between profound intoxication and complete recovery resembles more closely a chemical reaction *in vitro* than a biological reaction *in vivo*. In so far as we may consider the involved tissue as being isolated from the general circulation, as Kline and Winternitz have pointed out, the process must of necessity be largely local in its origin and effect. Recovery must be coincident not only with the destruction of the bacteria but also with the removal of the great mass of fibrinous and cellular detritus. In all of its essentials it is therefore an autolytic process and our hopes of therapeutic influence must be based not only on the idea of overcoming the infecting organism but also of favorably influencing the autolytic changes. The very isolation of the lung tissue from the general circulation after the disease process has once made headway favors

autolysis, for if the tissues were freely supplied with blood serum, with its greatly increased antiferment, autolysis could not take place. We can on this basis understand that the pneumonic process, apart from complications, will tend to be a short and self-limited one, for even if the invading organisms are very virulent and kill off the leukocytes in the alveoli, their very destruction will liberate protease and when digestion is commenced, terminate the disease.

But the crisis, although as a rule associated with the disappearance of the organism, need not on this basis at all times imply that the invasion has been overcome. The one is a physicochemical process, in the other we deal with an immunity phenomenon. Blake and Russell describe two experimental observations that are illustrative of precisely this condition—one instance of recovery by crisis in which the blood culture remained positive for 48 hours after the crisis and clinical recovery; the others were cases with crises on the 7th and 9th days, respectively, then normal temperature for several days, followed by a rise in temperature and death of the animals. At autopsy a resolving pneumonia was found; death in these cases being due to a persistent pneumococcus septicemia. Clinically such cases are occasionally encountered. They conclude that their results are "not out of harmony with the theory of Lord that other important factors besides the development of humoral antibodies are necessary to bring about recovery. It is not unreasonable to consider pneumonia as comprising two distinct though intimately related processes, one always present being the local lesion, the other, present in a variable number of cases, being a general infection of the body as manifested by the occurrence of a pneumococcus septicemia. Though ultimate recovery must primarily depend upon the ability of the patient to prevent or terminate the general infection once established, presumably through the existence or the development of humoral immunity, it does not follow that recovery from the local process with resolution of the pneumonic consolidation need be either coincident with recovery from the general infection or dependent on the same mechanism. In fact it would seem well established by numerous clinical observations that recovery from the general pneumococcus infection when it exists usually precedes, by several days at least, recovery from the disease at the time of crisis. On the other hand certain of the observations cited above would seem to indicate that recovery from the local process as shown by a rapidly resolving pneumonia may occasionally occur prior to recovery from the general infection, or even when death from the general infection subsequently takes place. In view of the above considerations it would seem not improbable that at least a dual mechanism may be concerned in bringing about final recovery from lobar pneumonia." The cultural experiments of Thomas and Parker lend support to this view.

Now let us observe the effects of the nonspecific reaction in this disease.

In the case illustrated in Figure 7 the patient was admitted to the hospital on the 5th day of April, 1917, with a history of illness for 5 days previous to admission. The diagnosis on examination was a frank lobar pneumonia of the upper left lobe. Two days after admission he was given a small dose of typhoid vaccine intravenously (25 million) following which he experienced a slight chill, some rise in temperature and then a fall in the temperature until the next day when it remained normal for several hours in the morning. After this remission it rose again by the evening and then came down by lysis at about the normal time.

This, it may be as stated, is a typical result, and portrays the experience that we have had when small doses of vaccine are so administered. There are usually a moderate chill (not as severe as in typhoid, for example), a slight rise in temperature, then a critical drop in the temperature and a normal temperature curve for several hours. Usually the former or a temperature slightly lower than that observed preinjectionally is then maintained and the disease continues its unaltered course. Euphoria, a decided clearing of the sensorium, improvement of the pulse and of the vascular tone of the patient are commonly observed after the injection if it has not been too great in dosage. The physical findings of the chest are as a rule not altered.

Miller summarizes his experience with 15 patients so treated as follows:

"Fifteen consecutive patients with lobar pneumonia entering Cook County Hospital were treated by a single intravenous injection of typhoid vaccine. The dosage used was 30 millions, the minimum amount required to give a chill. All reacted by a rise in temperature and a leukocytosis. In nine patients the vaccine did not modify the course of the disease. In six, the patient was detoxicated following the injections. The pulse, temperature and respiration returned to normal, the cough and pleural pain subsided, and the patient stated that he felt much better. In three of the six cases the improvement was temporary, as after the lapse of from twelve to twenty-four hours the symptoms returned with unmodified severity. In three cases the detoxication was permanent; however, the patients had a moderate temperature for from three to four days, to the time at which the crisis would normally appear. They were, however, entirely free from evidence of intoxication. There was no relation between the severity of the chill, the temperature reaction and degree of increased leukocytosis, and the beneficial results of the vaccine."

One might characterize the changes as a temporary detoxication that leaves the general course of the disease process unaltered, a result that might be anticipated from the pathology. The biological alterations previously described, i.e., the enzyme mobilization, the

## PROTEIN THERAPY

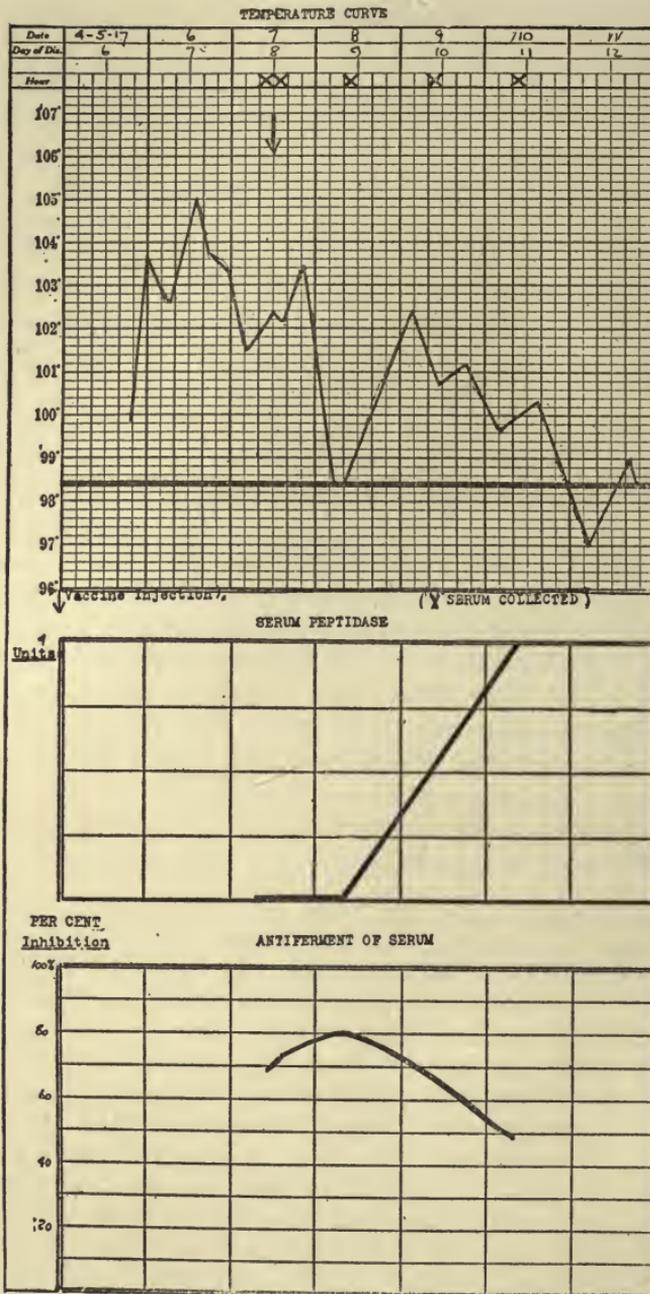


FIG. 7.—Serum ereptase and antiferment titer in pneumonia subject to vaccine shock.

alteration in the permeability of the capillaries and of the cells of the nervous system and the general plasma stimulation might lead to a detoxication of whatever noxious material might be present in the circulation, and the increase in the threshold of cellular resistance to intoxication lead to a state of relative detoxication so that the

patient would for the time being seem improved—have a lowered temperature, euphoria, increased vascular tone, etc., but it is hardly to be expected that the changes would be sufficiently great to effect the immense and relatively inert local disease process, isolated, as it in a measure is, from the general circulation. Here the production of toxic materials would proceed largely unmodified; these would accumulate, would finally get out into the general circulation to a sufficient degree and again produce symptoms of general intoxication.

If pneumonia were a disease characterized by a long incubation period, during which there would develop not only sensitization to the protein of the invading organism but in which the beginning of immunization could take place, then nonspecific therapy—plasma-activation—might aid in the process of shedding the preformed antibodies—would possibly mobilize them and so bring about recovery. But beginning as it does without an incubation period of any extent this factor is not involved in the mechanism. From the single large dose we can therefore expect little result other than a transient one. But of course there are exceptions. One such may be of interest in this connection. It concerned a boy of 12 years brought to the hospital after one day's illness with a frank lobar pneumonia of the upper left lobe. The interne, using typhoid vaccine as a routine, by accident injected a large dose (500 million organisms) intravenously. The child reacted with a severe chill, the temperature increased to 107° F. and he became delirious. The next morning the temperature of the patient was normal, and remained so without further fluctuation. All physical signs of consolidation had disappeared within 24 hours after the injection. Naturally the production of such a severe reaction is wholly unwarranted as a clinical method and the results are merely mentioned to illustrate that while it may in rare instances be possible to alter even the large pulmonary processes, such a result is quite uncommon.

Of course, when we are dealing with a bronchopneumonia the conditions differ to some extent. So, too, the possibility that repeated small injections used as stimulants (plasmaactivation) may be productive of favorable results need not be discussed in this connection.

**Sepsis.**—When now we come to the diseases characterized by a true multiplication of bacteria in the blood stream and observe the abrupt termination of such septicemias that have been recorded following the intravenous injection of the nonspecific agents (Werner, etc.), the problem becomes one of decided complexity. Our effect on local inflammation falls away, we must deal wholly with the destruction of bacteria multiplying in the blood stream. Here, too, the mere detoxication of the patient that has been discussed in connection with pneumonia, is not the total effect of the injection. This detoxication, the result of the vascular and cellular alterations in permeability, of enzyme stimulation, etc., is of course apparent in septicemia as well as

in pneumonia, but the occasional abrupt termination of the disease, the destruction of the invading parasite, is an additional factor that must be accounted for.

That foreign protein injections have an influence on the course of a sepsis even in experimental animals has recently been demonstrated by Weichardt. In a series of mice injected with streptococci he found that if injections were made before the streptococci were injected, or as late as 24 hours after the injection, there was no appreciable difference between the protein and the control animals; if the foreign protein was injected from 4 to 8 hours after the infecting dose of streptococci a definite effect on the duration of life of the mouse was apparent.

It seems probable that in this condition the effect on the leukocytes and on the antibody concentration is of greater importance than in the disease processes heretofore discussed. Where the body has been infected for some time the cells have as a rule become sensitized, have within them an increased amount of receptors, fixed antibodies. If these, as a result of some "shock," are thrown into the circulation the body cells will become less sensitive, not being able to fix the same amount of antigen; on the other hand the antibodies now free in the blood stream are able to affect the bacteria. The augmentation of the agglutinin and opsonin titers in particular will be of value in clumping the bacteria so that they will tend to accumulate in the great filtering centers of the blood stream—such as the spleen, bone marrow, liver, etc. (Bull.)

In addition to this fact we find that the coincident effect on the leukocytes in the reaction following the nonspecific reagents is a primary leukopenia that lasts for a variable period of time, but usually for several hours. This does not represent a destruction of leukocytes, but merely the accumulation of the cells in the internal organs—lungs, liver, spleen, bone marrow, etc.

We deal here with two factors that by simple mathematical reasoning (the increase of proximity) favor phagocytic destruction of bacteria—the accumulation of bacteria, clumped and opsonized, in the blood filters—the accumulation of polymorphonuclear leukocytes in the same locations.

While these processes are operative, the direct stimulation of the hematopoietic organs may be of value. The proliferation of leukocytes as indicated by the number of young forms (Arneeth count) that are to be observed in the circulation after nonspecific reactions would mean that where the bacteria have accumulated and clumped—the bone marrow, spleen and liver—these younger leukocytes, presumably active and of enhanced phagocytic power, would encounter the invading organisms and engulf them.

If we survey the mechanism in the various pathological processes that we encounter, in strictly local inflammations (bubo), in localized lymphatic infections (typhoid), in localized organ involvement

(lymphatic, interstitial and external) as in lobar pneumonia, or finally in true septicemic conditions, we find that no one factor can be identified in the mechanism as of paramount importance.

In the local reaction the alteration of the permeability of the cells and the complex changes in the inflammatory reaction that this entails seem of greatest importance, together with the detoxication of toxic proteins by the acceleration of enzyme activity.

In the typical lymphatic involvement represented by typhoid fever the increased permeability of the vessels and the flushing of antibody rich fluids into the lymph spaces, the desensitization of the patient as a result of later cell membrane changes and the general increase in cellular activity, in vascular tone, in the tone of the central nervous system, etc., are perhaps the more important factors.

In pneumonia, on the other hand, we may be able to overcome the effect of the intoxication for a temporary period by increasing the enzymatic rate of destruction of the toxic proteins, as well as by increasing the resistance of the cells to the toxic effect, but we are not able sufficiently to alter the physicochemical balance that exists in a more or less isolated lobar lesion, and on which the inception of the crisis depends. Here, then, we have to deal largely with a transient detoxication.

In the true septicemias it seems more probable that, apart from these factors that tend to diminish intoxication—that is, the enzyme mobilization and the decreased permeability of the cells—the actual destruction of the invading bacteria must be due to leukocytic digestion and perhaps the direct effect of the serum antibodies mobilized. The clumping of the bacteria and their accumulation in the internal organs and bone marrow bring them in closer proximity to the leukocytes, which, as a result of the injection, have also been concentrated in the internal organs and bone marrow.

It is at any rate apparent as a result of these considerations that different disease processes are diversely affected by the nonspecific agents, depending on peculiarities of localization, on the source of the material that is responsible for the intoxication, on the degree of sensitization and immunization of the patient. While nonspecific agents may produce a reaction that is fundamentally alike, the effect on different disease processes may differ considerably.

## CHAPTER VII

### THE RELATION OF THE SKIN TO NONSPECIFIC RESISTANCE

**Skin Reactivity.**—The fact that the skin and its reactivity can be influenced by a variety of systemic pathological changes and through therapeutic procedures has been observed by physicians for many centuries, indeed ever since counterirritation by means of blisters and chemical irritants was introduced (about 1600 A. D.). "We often find in cases of intense irritation of internal organs that blisters will not vesicate the skin, but that as soon as the disease is modified they will produce their usual effect," wrote Stokes (as quoted by Gillies). Translated into our more modern procedure we find this same phenomenon observed when we apply the tuberculin reaction to the skin of a patient during any acute disease, or in pregnancy or in cachexia, and note that the reaction, normally obtained in practically every adult, has disappeared.

It is not needful in this connection to review more than briefly recent ideas that have been advanced by a number of observers concerning the direct reactions of the skin to various stimuli, or the change of the skin activity following certain general alterations of the organism. It is known that the tuberculin reaction cannot be elicited during acute infections, pregnancy, cachexia, serum disease, etc.

Similar observations have been recorded for vaccines. Thus Matthes and Rautenberg have recently shown that the digestion products of typhoid bacteria which were used as a vaccine have a far greater local effect in the normal individual than in those ill of typhoid fever.

Hoke, working with the intracutaneous test, found that the traumatic reaction, as well as the intracutaneous tuberculin reaction, were increased in leukemia as well as after thyroid feeding, while in cases of cachexia, in fever, in local infection and in deeply pigmented skin the reaction was diminished.

**Depression.**—Certain general conditions of the body, quite diverse in their origin, are able to suppress the reactivity of the skin to tuberculin. These general conditions are obviously not specific; that is, they need bear no relation to tuberculosis, nor do they alter the antibodies and in this way effect the tuberculin reaction in a specific manner because it has never been shown that there is any parallelism

between antibody content and skin reactivity. Then it was observed that the reactivity of the skin could be inhibited by injections of various kinds—the heterologous and homologous serums, colloidal metals, starch, in fact after nonspecific injections of various kinds.

Luithlen took up the experimental study of the alteration of skin reactivity from the vascular side. Using croton oil as an irritant he has observed that after the injection of normal serum of any kind—homologous and heterologous—after plasma injections or blood transfusion, after gelatin or Witte peptone, after colloidal silicate and after starch injections the reactivity of the skin was markedly depressed. Crystalloids did not alter the reactivity, in some instances actually seemed to increase the reaction. Luithlen soon recognized that this alteration had nothing to do with any commonly recognized biological or antibody action on the part of the serum, but was due to an alteration produced by practically every colloid injected.

This change he considered dependent on an alteration in the permeability of the capillaries. In determining this change in permeability he proceeded as follows: Rabbits were injected with Ringer's solution intraperitoneally (100 c.c.) and then 2 c.c. of a 10% solution of sodium ferrocyanid was injected intravenously. The rate at which the ferrocyanid permeated the Ringer's solution in the abdominal cavity was then determined by adding hydrochloric acid and ferric chlorid to samples drawn from the peritoneal fluid at various time intervals and noting the time when the first blue coloration was obtained. The normal time was about 2 minutes. Similarly the permeability to sodium iodid was determined and found to be about 1 minute. Variations were noted with the age of the animal and its state of nutrition.

When such animals were now injected with the various colloids which had been found to depress the reactivity of the skin, it was found that they all decreased the permeability of the capillaries as measured in the manner that has been described. Salts did not alter the rate of permeability very much, but repeated bleeding had a definite effect on diminishing the permeability.

*Activation.*—If the reactivity of the skin can be altered in the sense of a depression we must accept the corollary that nonspecific factors may possibly be able to accelerate the cutaneous reaction. And of this we have abundant evidence in the effect of thyroid feeding and of iodid therapy to which Sherrick called attention some years ago and which has been confirmed and amplified by a number of other workers—Kolmer, Sollmann, Stokes, etc.

We are therefore led to the inevitable conclusion that elements wholly nonspecific in our ordinary sense of immunological specificity may be of decided importance in the mechanism of the skin reactions.

Clinically, too, we have been forced to the same conclusion as a result of observations on a variety of skin reactions which have been

elaborated during the course of the past ten years. Not only was the luetin reaction found to be unreliable when iodids were administered but even with these excluded the specificity of the reaction is by no means to be depended upon. Thus Blechmann has but recently published a series of 80 cases in which he injected luetin. In this group of children his luetin was positive in about 35% of the congenital luetics, while in about 40% of nonluetetic children he also obtained a positive luetin test. So, too, the typhoidin reaction has been found an absolutely unreliable index of the immunity of the patient. Other skin reactions, such as the gonococcus reaction, the placental reaction for pregnancy and the pneumococcus reaction, have failed for the same reason. Only where we deal with a disease depending very probably on a definite hypersensitization of the patient, such as in asthma, are the skin reactions useful.

When skin reactions are under consideration one inevitably thinks of the tuberculin (either the v. Pirquet or the intracutaneous test) reaction as the most typical and best known of the whole group. The general reaction—subcutaneous injection—should by no means be considered in the same category. It is very probable that the tuberculin reaction, which for ordinary clinical purposes we may consider specific, has a very large element of nonspecificity in its mechanism—much larger than is ordinarily considered probable, as has been fully discussed in the chapter on The Focal Reaction. Such a phenomenon would by no means be an anomaly in medicine; indeed our Wassermann reaction is an example of just this same condition. Elaborated on a theory of strict specificity it has resolved itself into a specific clinical test that is based on a physical mechanism in which the antigen-antibody reaction plays no part. We must recognize, too, that the evanescent reactions or wheals that we observe in determining sensitization to proteins (asthma, etc.) are fundamentally different in many respects from the tuberculin reaction.

Clinically it has been determined that from the time of the birth of the individual the organism begins to alter in its reactivity of the skin. At first negative to tuberculin, the reactivity increases progressively with the age of the individual until in adult life a maximum is reached and maintained quite consistently except for certain periods of depression, some of which have been previously mentioned. But during this period the skin does not only become sensitive to tuberculin, but increasingly sensitive to a series of other bacterial and plant proteins and extractives; so to colon and dysentery and cholera proteins, to bacterial toxins, peptones, etc. We deal obviously with a more or less general "sensitization" or "Umstimmung" or "allergy," as we may choose to term the condition.

Now, this allergy may be a more or less specialized property of the skin, indeed may be localized in certain areas of the skin. As a result of it the tissues acquire the ability to react more energetically and

more promptly to outside stimuli—whether specific, as with tuberculin, or nonspecifically as when other proteins are injected in and about an area previously injected with tuberculin, or finally when substances nonprotein in character such as sugar or starch are used. (Stokes.) Even those investigators who have heretofore been the most ardent advocates of the specific character of the tuberculin reaction, such as Wolff-Eisner, have been compelled to accept the inevitable conclusion that in the tuberculous individual the skin (and the body as a whole) is hypersensitive not only to tuberculin but to proteins in general.

In a paper published with Sexsmith we have pointed out a possible basis on which some of the clinical experiences as well as the conflicting experimental data might be more readily understandable.

**Enzymes in Skin Reactions.**—Considering both the phylogenetic and ontogenetic development of the skin and its function it is apparent that its power to secrete enzymes is one that is more or less inherent in the epithelial cell—ultimately highly specialized and differentiated in some of its developed organs, rudimentary and potential perhaps in the structures that serve later primarily for protection rather than in the active metabolic processes. As a protective structure its efficacy will depend to a large extent on its ability to react both very rapidly and very strongly against either invasion or intoxication. When one examines the enzymes of the skin one observes apparently a decided difference in the enzymes of the infant or young skin as contrasted with the adult. The young skin contains more ereptase (erepsin or peptidase) and little lytic protease; the adult skin on the other hand little ereptase and more protease. Neither type of skin contains much antienzyme.

Let us suppose that we inject peptone into the young skin. The ereptase could immediately detoxicate the material injected and there would be no necessity for an inflammatory reaction. If we inject a native protein which only becomes toxic when it is split, the infant skin (containing less protease than the adult) is not able to split the protein, no toxic products are formed and there is no reaction. Indeed the action of whatever protease is present in the young skin seems decidedly synthetic rather than lytic.

If now we examine the picture in the adult we find the exact reverse. If a peptone is injected there is little ereptase present to detoxicate it and the material is present in the tissues long enough to set up an inflammatory reaction. If on the other hand we use the native protein the presence of sufficient protease in the skin will permit the same to be broken up with the formation of protein split products toxic to the cells and an inflammation will be the result. The relative paucity of ereptase will here delay the detoxication.

Inasmuch as our ordinary agents that we use in eliciting skin reactions are usually mixtures rather than pure protein or protein

split products the enzyme reaction will seldom be as clear cut as here portrayed.

But why the tissues react more readily the second time is a question that is of such vast biological significance that we can merely surmise some of the more superficial and obvious alterations that are involved. Even were we to consider nothing but antibody reactions in the immunological sense recent work would indicate that this alteration—*allergy*—is not necessarily specific. Bieling has demonstrated that any primary sensitization leaves the body in a state of high grade hypersensitiveness. Animals immunized to cholera, for instance, required but a minute fraction of the ordinary dose of typhoid antigen to bring about a high degree of immunity to typhoid. The fact that a secondary injection of a heterologous protein or other nonspecific agent will mobilize the antibodies formed against a previously injected antigen is of course well known and has been extensively studied by Bieling, Hektoen, Johnson and others. The cell has been so altered that its reactivity is increased, as though a dull instrument had been suddenly shaped to razor-like keenness. To what degree this involves more or less permanent alterations in the physical make-up of the cell ectoplasm, in how far the protoplasm of the cell is involved, is of course purely speculative.

We must go back for a few moments and consider the possible mechanism of the suppression of the skin reactivity to which we have called attention in relation to certain conditions, such as pregnancy, acute infectious diseases, cachexia, etc. If in the nonspecific enzyme action that goes on in the skin the proteolytic activity can be suppressed, then intoxication and inflammation that is due to the splitting of native proteins to the toxic forms should also be inhibited. Such inhibition can take place when the chemical reaction of the medium is not suitable or when we have an excess of antiferment present. All of the states during which the skin reactions are suppressed are conditions associated with an increase in the titer of the serum antiferment. Stern made a careful study of the suppression of the tuberculin reaction during pregnancy, when the antiferment titer of the serum is of course greatly augmented. Blöte confirmed this work and showed that this was by no means a specific phenomenon because when he used an extract of jequirity in place of the tuberculin he obtained a similar result. This increase in the antiferment titer which occurs after nonspecific injections of various kinds, after serum sickness, during antianaphylaxis, is coincident with the alteration in the permeability of the capillary endothelium to which Luithlen, von den Velden and others ascribe the alteration in the skin reactivity and which must also have a large share in the mechanism.

Meyer has studied particularly the inhibition in the cutaneous reactions to tuberculin which takes place after prophylactic typhoid vaccination. Here, too, we deal with a nonspecific reaction, with an

increase in the antiferment titer, alterations in the permeability of the vessels, and temporary depression of the irritability of the vasomotor system and central nervous system which lasts for a period of a week or so after the injection.

The converse of this clinical observation has to deal with the reactivation of skin foci by nonspecific injections after they have undergone involution. Thus it has been observed that old tuberculin papules will become active when a subcutaneous injection of tuberculin is given in some remote area of the body, when milk is injected or colloidal metals injected intravenously. To what degree elements of specificity enter into this reactivation is by no means determined. Munzer observed that when partial antigens (Dyche-Much) were injected they would often reactivate old intracutaneous tuberculin papules while milk injections did not have this effect.

Closely related is the effect of the iodids and other chemical agents which on administration activate involuting papules. If intracutaneous skin tests are made with luetin or tuberculin during active iodization of the patient, the skin reaction, instead of being limited to mere papule formation, usually goes on to the complete pustule stage of inflammation. Now the iodids act, as do the related chemical agents, either by lowering the antiferment titer (Jobling and Petersen) or by nonspecifically stimulating the tissues (and so increasing the amount of protease and other enzymes in the tissue fluids) or finally because of their effect in hastening the rapidity of diffusion of other salts (and colloids) in colloidal systems. The end result is of course the same—digestive processes are hastened. The two other conditions—leukemia and thyroid feeding—in which the skin reactivity is increased are associated with a diminution of the antiferment titer and an increased enzyme activity.\*

When, therefore, involuting papules flare up under nonspecific injections we must consider the possibility that the following changes may form the basis of the inflammatory reaction. With the height of the nonspecific reaction (negative phase—digestion) a considerable amount of protease is mobilized locally and generally and the antiferment is diminished. If in an involuting area a certain amount of undigested protein material is still present, digestion will commence, protein split products will be liberated at the focus and the lesion will again flare up—that is, we will witness a focal reaction. The local cells, it is to be remembered, are particularly reactive in such a condition.

When the patient is iodized and an intracutaneous test made we seem to deal simply with a condition where digestion has been able

\*The fact that iodids may have no direct effect on tissue autolysis *in vitro* as Albrecht has recently demonstrated has no direct bearing on the point at issue which *in vivo* concerns rather the mobilization of protease from normal tissues and their effect on tissues that have undergone degenerative change.

to proceed much farther and more rapidly than in the uniodized patient. When the injection is made a certain amount of tissue injury is done. Some of the cells will be injured both from the trauma and from the toxic material injected. In the uniodized patient the inhibition of digestion due to the antiferment checks autolysis to a degree, the process is delayed sufficiently so that no great amount of split products are present at any one time. The rate of formation will not exceed the rate of diffusion. In the iodized patient, on the other hand, the rate of digestion being greatly accelerated, protein split products will accumulate in the cutaneous tissues in an amount greater than the rate of diffusion, more tissue injury will be done; with autolysis leukocytes will be attracted and a pustule will result where under ordinary circumstances merely a papule would have been formed, or a papule will result in an individual in which the reaction normally would have been absent.

While from these observations it is apparent that nonspecific factors can undoubtedly influence the tuberculin reaction or the other skin reactions both in the sense of depressing them or accelerating the reactivity of the skin, we must by no means lose sight of the fact that a specific element enters into the cutaneous reactivity. In my opinion it is probable that the explanation for the fact that the tuberculin reaction is clinically specific and fairly reliable while similar skin reactions (typhoidin reaction, etc.) are not, is to be found in the fact that the tuberculous individual, because of his continuous absorption of proteins, is in a state of generally increased sensitiveness to proteins. This hypersensitiveness is of a degree sufficient in tuberculosis to overbalance the nonspecific factors which in other diseases interfere so greatly that the interpretation of the skin reactions becomes both difficult and unreliable.

**The Relation of the Skin to Internal Medicine.**—While in a general way these studies have been undertaken from the point of view of the dermatologist, a wider viewpoint that includes the relation of the skin and its reactivity to problems in internal medicine has found expression in a number of papers. Particularly the study of the various diatheses has interested a group of investigators. Thus Schulz, using dilutions of carbolic acid to bring about skin reactions, determined that children with exudative diathesis usually revealed an increased irritability of the skin. It seems probable that the severity of the vaccina reaction and the reaction to the parenteral injection of proteins that such children often show is to be associated with this change. But the hypersensitiveness, according to Schulz, is not limited to children; many adults suffering from eczema have been found by him to be decidedly hypersensitive.

Brocq's investigations in this connection are of importance. It has been Brocq's contention that in such hypersensitive individuals—and

families—there exists a so-called “arthritic milieu” as a result of which they are particularly susceptible to a variety of pathological alterations. They react to outside trauma or stimuli of such mild degree that would, in the normal individual, provoke either no response at all or at the most a very negligible reaction. Eczema, lichen, urticaria, food and drug idiosyncrasies, herpes, furunculosis, pruritus and psoriasis are regarded by him as belonging in this category. To it he also adds hay fever, asthma, gout, adiposity, migraine and neuralgia. Even Bloch accepts the first five of the skin diseases as belonging to this “arthritic” group of diseases. The French clinicians have carried this conception to its logical conclusion and do not speak of eczema as a disease entity but of “eczematization” (Besnier, Darier, Rapin and v. Hirschberg, etc.).

It is by no means excluded that this sensitization takes its origin from some primary bacterial infection—tonsil, gastro-intestinal (gall bladder and appendix) or respiratory.

*Esophylaxis.*—The association of skin reactivity and internal conditions has recently been illustrated in experiments of a different nature. During the course of investigations on the mechanism of intoxication and death from burns, Pfeiffer observed that a marked mobilization of proteolytic enzymes occurred after even superficial burns of the skin. As a result of this observation and others closely related he felt justified in including the intoxication of burns among those due to protein split products. In view of the relatively rich enzyme content of the skin such a mobilization after stimulation might be anticipated. But in so far as this mobilization, when it is within physiological limits, or under therapeutic control, may play a rôle in influencing internal diseases, the study of the skin reactivity becomes of interest to us not only in the sense that it protects against disease entrance—an “exophylaxis,” as Hoffmann has termed it, but because of its importance on the internal organs as well—an “esophylactic” effect.

Bloch and Hoffmann have both discussed this subject in recent papers which seem of considerable interest in connection with the mechanism to which attention has been called. Bloch has expressed the conviction that the skin possesses a biological function, heretofore unappreciated, by means of which the vital organs are protected from bacteria, or at the most have but to deal with a minute amount of attenuated bacteria. Taking into consideration the more recent work concerning the phenomena of allergy as observed in tricophyton infection, in tuberculosis and syphilis he emphasizes the fact that “the skin above all other organs plays a leading rôle in allergic immunity and sensitization, as contrasted with serum immunity, such as that of diphtheria, tetanus, etc., where the serum is the carrier of the anti-disease mechanism.”

The allergic alterations—vaccination against variola—the funda-

mental observations of Koch on the production of tubercles in the skin, which, in the infected animal, assume a much stormier and rapid course—the researches of v. Pirquet on the vaccination allergy in tuberculosis, syphilis, and fungus infections—all point to the skin as fundamentally involved in the mechanism of resistance. Perhaps it plays some rôle even in recovery in the acute exanthemata, such as measles and scarlet fever; in variola its importance is obvious. Heim has recently expressed the opinion, which was current many years ago and still is more or less popular in folk medicine, that the skin eruption of the acute exanthemata is involved as part of the mechanism of recovery. His conception is that the organism endeavors to rid itself of the toxic substances through the skin, that a leukocytosis occurs there and that the latter is of utmost importance in digesting the toxic material. While in bald outline the theory may seem crude, it is possible that there may be some connection, as Heim has suggested, between the skin eruption and the mechanism of recovery, as I shall endeavor to point out later.

Hoffmann calls particular attention to the clinical observation that the internal organs are frequently spared from serious involvement both in syphilis and in tuberculosis when the skin lesions are extensive. In order to emphasize the importance of the skin in its relation to internal medicine he calls attention to a number of other facts that are more or less pertinent. The fact that an intoxication ensues when large areas of the skin are put out of function by varnishing or burning; that the large bulk of epithelial tissue, with its elaborate network of intercellular canals and its proximity to the vascular corium would facilitate absorption of secretions; that the folklore of many generations expresses the idea that in the exanthematic diseases the internal organs are spared to the degree that the eruption is manifest in the skin, with the therapeutic conclusion that anything that will increase the eruption influences the patient favorably (Heim also calls attention to this tradition), all indicate, even if only in a general way, that the skin may be of importance in overcoming infection.

*Hoffmann's Theory.*—Hoffmann makes the epigrammatic statement that “the skin is the grave of the parasites.” The fact that so many acute infections involve the skin—measles, scarlet fever, variola, typhus, syphilis, etc.—has led him to the conclusion that the skin plays some active rôle in immunity. In how far some internal secretion of the epithelium, to what degree the vascularized papillary body with its ready inflammatory response enters into this mechanism, he does not suggest. This ability to respond readily with inflammation might be anticipated both from the phylogenetic as well as from the ontogenetic development. Thus the skin of the adult reacts more rapidly and to a wider range of substances than that of the infant, the skin of the human more readily than that of lower animals.

*Light Rays.*—Perhaps the effect of light on the skin and the recent

use made of this effect in the therapy of internal disease is of particular interest in disclosing the degree to which the skin reactivity can make its influence manifest on the metabolism of the internal organs and pathological processes there present. When a patient is exposed to light rays in the manner developed by Bernhardt, by Rollier and others, certain systemic changes occur which in many ways resemble very closely the reaction that we have described for the protein shock reaction or the nonspecific reaction. Rollier observed an increase in eosinophils as well as in hemoglobin and red cells. D'Oelsnitz observed changes in the temperature, in the respiration and in the blood cytology. The temperature and the respiration are both increased at the beginning, the pulse rate may be accelerated to some extent—all of the reactions depend greatly on individual factors and particularly on the disease from which the patient is suffering; in tuberculosis, particularly on the type of the tuberculous lesion, whether active or latent, etc. The leukocytes that are produced are usually young forms, although in the reaction mononuclears predominate; eosinophils were also observed by D'Oelsnitz.

*Dual Effect of Heliotherapy.*—Just as in other nonspecific reactions the effect of the sunlight on the skin and the effect on pathological conditions is a dual one. Thus it may activate an inflammatory focus. In active progressive tuberculosis with hemorrhage and a septic type of temperature, exposure may do decided harm. In its general effect the reaction set up is similar in character and duration to that elicited by tuberculin and the contra-indications are the same. Thus a latent tuberculosis on exposure to prolonged sunlight may react with a typical temperature, increase in pulse-rate and the general malaise that we associate with the tuberculin reaction. And just as it is a dual reaction the negative phase is followed by a positive one. That is, the difference between irritation and stimulation and overstimulation is a matter of very small margin and depends on the individual, as Pottenger has pointed out. Sunlight has no specific effect on tuberculosis; it is not a cure in the ordinary sense of the word. It is merely a stimulant similar in character to many of the other nonspecific agents which are able to cause a focal reaction and thereby influence the process. Its difference from some of the other forms of therapy lies in the fact that the leukocytic response that follows heliotherapy seems to be rather a lymphocytic than a polymorphonuclear reaction. In nontuberculous affections it has been recommended in general convalescence, where it is followed by an improvement in the anemia (effect on hematopoietic system) and in the weight of the patient. Aimes has found it very useful in acute articular rheumatism, in tracheobronchial adenopathies and in neurasthenic patients. (Kellogg). Lovett has reported excellent results in chronic infections.

*Heliotherapy as Protein Therapy.*—It seems most probable that instead of seeking to find the cause of the therapeutic effect of the

sunlight in some hypothetical internal secretion of the skin which is stimulating the entire organism, it will be found much simpler to consider that the effect of the sun raying of the skin tissues brings about a mild (or severe, depending on the degree) form of nonspecific shock. We know from Pfeiffer's work that actual burns will do this. Between the erythema of a burn due to actual heat and that due to sunlight there is not much difference as far as the patient or the effect on the organism is concerned. The epithelial tissues become hyperemic and absorption from them is accelerated. Skin enzymes—protease and lipase, perhaps some ereptase in younger individuals,—are swept into the circulation, together with some protein split products due to digestive stimulation in the skin. The agents that ordinarily provoke the nonspecific reaction are therefore available—the enzymes present in the serum can now attack seminecrotic or necrotic foci and there accelerate the preëxisting inflammatory reaction—i.e., set up a focal reaction—a tuberculin reaction—with its resulting train of increased temperature, malaise, etc. As a result of the protein split products derived from the skin the organism is of course stimulated in the typical nonspecific manner and the effect on the hematopoietic system, on the irritability of the nerves (Singer, Pottenger), on the general metabolism, is similar to that which we have seen with the other nonspecific reactions. Differences exist in the type of leukocytic response, which seems to be more lymphatic in the case of heliotherapy. Another possibility of particular value in tuberculosis may be found in the relative richness of the epidermal tissues in lipases which, when mobilized after heliotherapy, might, theoretically, prove of decided value in resistance to tuberculosis.

The effect of heliotherapy in causing a focal reaction can best be illustrated when one follows the effect on a tuberculous focus such as an area of lupus. Even when all direct effects of the rays are excluded by means of black paper, a lupus lesion will react with a typical focal reaction after a general sun bath just as it does after tuberculin injection, after milk injection or any of the other nonspecific agents. Tuberculous foci have been observed to become much more "sensitive" or reactive to other stimuli such as *x*-rays or concentrated red rays, etc., after general heliotherapy.

*Local Applications.*—Hoffmann calls attention to the fact that other therapeutic measures, soap inunctions, mustard baths, sweating, counterirritation, etc., may involve precisely the same mechanism. When we examine the acute exanthemata from this point of view, it will become apparent that the skin manifestations and their severity may well have some influence on the general course of the disease. Granted that the nonspecific reaction produced by injecting various substances may terminate an infectious disease abruptly—and the clinical evidence is sufficiently varied by this time to permit such a general statement—we have seen that it is immaterial how this reaction is elicited.

For therapeutic effects certain agents have been found more effective than others, but within certain limits they are all more or less effective.

*Acute Exanthemata.*—If in an acute exanthema we regard the huge skin involvement in the nature of an inflammatory reaction, it follows that from it not only enzymes but toxic split products are being absorbed very rapidly when the hyperemia that is part of the inflammatory reaction becomes pronounced. When the skin reaction reaches its height we know that it is accompanied clinically by an increase in the temperature and that defervescence usually follows in the wake of this increase. The normal mechanism of recovery in these acute diseases may therefore involve precisely the same nonspecific reaction that we now seek to make use of therapeutically in other conditions.

In variola the appearance of the skin eruption is of course coincident with the improvement in the general condition that is so characteristic of the disease—the lowering of the temperature, the pulse rate, the pronounced euphoria, etc.—and the secondary fever is purely an absorption fever when suppuration sets in, similar in its character and course to that of any other suppurative condition.

**Focal Activation from Intracutaneous Injections.**—Perhaps one of the most striking illustrations of the importance of skin stimulation and its effect on remote disease processes is afforded by the recent work of Müller. The interesting fact has been brought out by him that the intracutaneous dosage required to bring about a focal activation may be 1/30th less than the dose required if given intramuscularly or intravenously, and it is of course immaterial what agent is used in the skin injection. Thus he found that “arthigon,” typhoid and cholera vaccine, tetanus or diphtheria antiserums and even salt solutions were able to elicit focal provocative reactions as tested in gonorrhoeal urethritis. His results emphasize the fact that relatively minute and seemingly insignificant skin reactions may exert a tremendous effect on remote pathological lesions and that we must seek the mechanism of this phenomenon in metabolic alterations produced in the skin, not in peculiarities of the agent that we happen to use to bring about the reaction. Needless to state, the tuberculin therapy of Ponndorf (which consists of intracutaneous injections of tuberculin) is related to the alterations that Müller has studied. And, as we might expect, a variety of clinical conditions have been reported to improve after the Ponndorf technic. Thus Kroschinski found that neuralgia, neuritis, tabetic pains, acne and furunculosis responded to the tuberculin injections made in this manner.

**Syphilis.**—When now we turn to examine the clinical statement that is often made, namely that in syphilis accompanied with extensive skin lesions, or in tuberculosis that has its chief site in the skin, the internal organs are as a rule free from pathological changes, we find considerable evidence of a clinical character to support the assertion.

General paralysis, tabes and tertiary lesions are said to be very uncommon in countries in which the skin lesions are most manifest; racial differences seem to play some rôle, too, in the variation of distribution. In our American negro it is stated that the parasyphilitic manifestations are less frequent than in the white race, although vascular lesions are certainly common enough. According to some syphilographers even malignant syphilis, when in its early stages it is most manifest in the skin, is prone to spare the internal organs. According to a number of investigators the possibility must be considered that this effect is due to selective affinity of certain strains of the spirochete (Nichols, Matzenauer, etc.); Hoffmann would rather implicate the immunizing effect that is due to the early skin involvement. Clinically it has been shown that tabetics and general paralytics seldom give a history of severe luetic skin involvement; usually the history given is that the skin manifestation was merely transient and that there were no other secondary manifestations. Bloch assumes that it is the failure of the skin allergy that is the chief cause, particularly of nerve syphilis, either because of the constitutional inability of the skin to react or because the opportunity was not given the skin to react.

The wide distribution of the spirochete soon after it gains admission to the body would, in my opinion, rather exclude this latter explanation. But it must be remembered in this connection that the spirochete, or rather the reaction that the spirochete sets up in the tissues, is relatively easily influenced by nonspecific means. One has but to recall the effect of tuberculin on the involution of the syphilitic papule, the effect of the injection of colloidal metals (particularly silver) on the rate of proliferation of *Spirochæta pallida* in experimental animals, the effect of intercurrent diseases on the manifestations of syphilis, the pronounced effect of the iodids on the absorption of gummata and in the alteration of the skin reaction to luetin, etc. If the secondary lesion and the gumma are so easily affected by these means it is very probable that the inflammatory reaction in the skin, no matter how produced (even if by the specific inciting organism)—with its resulting absorption of enzymes and of protein split products—may act as a nonspecific agent and have some therapeutic effect on lesions located internally. It has even been suggested that the efficacy of the mercurial inunction over other methods of mercurial therapy is due to the fact that the skin is stimulated mechanically.

The fact that the tissues of the central nervous system afford a very favorable milieu for the spirochete when once it has penetrated must not be lost sight of. The meninges, being relatively easily penetrated by the spirochete, are infected early and often in syphilis. It is the ectodermal brain substance which has to bear the brunt of the spirochetal changes, for the pia, although early involved, seems to rid itself much more readily. Both the brain substance and the cornea, containing neither lymphocytes nor adventitial cells, react but poorly

to the spirochete, and the effect of syphilis is strikingly similar in both cases, as Gärtner has recently pointed out. Specific therapeutic measures have been found equally unsatisfactory in syphilitic lesions in both tissues.

If we are able to bring about a nonspecific stimulation we at times seem to be able to secure a much more prompt effect on the luetic lesion; the therapeutic application of the principle has been discussed under the respective subjects.

It seems probable that the clinical impression of increased resistance to syphilis on the part of the internal organs when skin involvement has been extensive may have some definite basis, in that a severe inflammatory reaction in the skin during the time of the invasion by the spirochete might, by nonspecifically stimulating the body, increase the resistance of certain of its tissues that normally are more susceptible to the spirochete. If this reaction occurs sufficiently early the virus might be prevented from gaining a firm foothold in the susceptible tissue and in this manner later parasyphilitic lesions might become less frequent in such individuals.

## CHAPTER VIII

### ARTHRITIS

The treatment of arthritis has been one of the most satisfactory fields in which nonspecific therapy has been applied. The contra-indications are few, the evidence of improvement is strikingly apparent to the patient as well as the physician, and the relief from the pain so welcome that the discomfort that may be involved in the method is usually willingly borne.

Miller and Lusk were the first to report on cases of arthritis treated with proteoses and with typhoid vaccine in their service at the Cook County Hospital in Chicago. This series of 24 cases gave promise of excellent results, and in a second paper published shortly thereafter they reported on the results in 85 additional cases.

Somewhat smaller doses of the typhoid vaccine (from 40,000,000 to 75,000,000) were given to their patients in this second series. They used proteose or pollen extract in a few instances, and the results obtained would indicate that with the proper dosage, improvement similar to that observed after the use of the typhoid vaccine would take place. In the second series there were 45 cases of acute arthritis, of which 4 were gonorrheal in origin; the period which had elapsed from the onset ranged from two to forty-five days. Previous to coming under the authors' care 33 had been under more or less active drug treatment, usually with salicylates. Of those who had been under previous drug treatment, 29 reported that they had not improved under this treatment, and 4 had been moderately benefited. With typhoid vaccine, 29 of the 45 patients recovered promptly; that is, the pain, redness and swelling disappeared in from one to five days, and usually within from twenty-four to forty-eight hours. From one to four injections were necessary to bring about these results. Of the remaining patients, 8 showed great improvement with only some stiffness or slight pain remaining. Six showed only moderate improvement; in 2 no benefit was derived from the treatment, although one of these received eleven and the other thirteen injections. Nine of the patients had recurrence, 5 of those discharged as cured and 4 of those discharged as improved. Seven of these were reinjected and either recovered or showed marked improvement. In the 4 acute gonorrheal cases in this series, less benefit was derived from the treatment than in those of other origin.

Twelve patients with subacute arthritis were treated; in 10 the condition cleared up in from three to five days after from one to four injections, although in 2 of them there was still slight stiffness or soreness in one or more joints at the time the treatment was discontinued, clearing up, however, a few days later. Two showed marked improvement after two or three injections, but subsequent injections failed to bring about further improvement. Among those discharged as cured recurrences were recorded in 2, 1 of these recovering after further injection; the other patient did not return to the hospital for further treatment.

Nine cases of chronic arthritis with marked acute exacerbation were treated and in 8 the acute symptoms cleared up promptly with from one to three injections.

Nineteen patients with arthritis of from a few months to several years' duration were grouped as chronic arthritis. Only those cases were selected in which there was definite evidence of activity, and ankylosis was not marked. Ten of these patients after from one to five injections showed a definite improvement, the acute tenderness and discomfort on motion was much relieved. The patients became less helpless. As a rule not all of the affected joints were benefited. The results, however, were such that it would seem the treatment had been actually beneficial. Not all of these cases have been followed, but there are several in which, after the lapse of several months, the improvement had been maintained. Five showed moderate improvement, and 4 were not benefited. The maximum number of injections given any of these patients was thirteen, being given daily in the beginning and later every two or three days. In 5 patients included in this group the arthritis was apparently of gonorrhoeal origin, and 3 of these showed such marked improvement that they might be pronounced as cured. This is in contrast to the resistance to the treatment of the acute gonorrhoeal cases. One of these gonorrhoeal cases was of several months' duration and for three months previous to entering the hospital the patient had been compelled to use crutches. After three injections he was able to get out of bed without assistance, and up to the present time (four months) has not had a relapse. It is the very striking results obtained in a few cases of this character which have led the authors to believe that in certain instances the results obtained cannot be equaled by any other of the present methods of treatment. The results in the cases of chronic arthritis are on the whole, however, not especially striking. The tendency to recurrence is great, perhaps owing to the persistence of a focal infection. It is essential, therefore, that where this method of treatment is employed, it be preceded by the usual efforts first to locate and remove the local infection.

The reaction provoked by the intravenous injection of the typhoid

vaccine was severe. There was always a very marked rise in temperature, and with few exceptions a marked chill. The headache as a rule was severe, and nausea of a few hours' duration was not infrequent. In 3 cases, all alcoholics, delirium developed at the height of the fever, in 1 case continuing for thirty hours. Marked dyspnea was observed in a few cases. In only 5 of their patients did Miller and Lusk deem it advisable, on account of the violence of the reaction, to discontinue the treatment after a single injection. No fatalities occurred as a result of the treatment, but it should be borne in mind that evidence of cardiac weakness or hypertension was considered a contra-indication to the treatment and such patients were not injected.

Scully later reported on another 24 cases of whom 40% cleared up promptly after a single injection and Thomas, working at St. Luke's Hospital, treated an additional 20 cases. Of these 30% were permanently relieved from pain.

Other American workers have reported on extended series of cases. Thus Cecil used the method in 40 cases, of which 26 were of the ordinary rheumatic type, 7 acute toxic arthritis and 7 of gonorrhoeal origin. Cecil gave typhoid vaccine intravenously, using a dosage of 30 to 100 million. By accident a few patients received a larger dose (400-500 million) but the reaction was not much more severe. Of the rheumatic and toxic arthritides 40% recovered completely in from two to ten days without the use of salicylates. The remaining 20 patients all received salicylates at some time of their stay in the hospital, either before or after their vaccine treatment. Of these 17 were cured or greatly benefited under the combined treatment. Cecil noted that while the pain in the joints was frequently completely relieved, a degree of muscular pain persisted in the muscles, particularly in the muscles of the back. The seven patients suffering from gonorrhoeal arthritis made very slow improvement by the vaccine treatment.

Cecil concludes that the method is undoubtedly efficient in many cases of acute arthritis, but that it is unpleasant for the patient and may be dangerous when administered to improperly selected patients. It is interesting to note that several of his patients developed herpes labialis following typhoid vaccines (we had the same experience with certain strains of vaccine; others never were followed by herpes). One patient developed delirium tremens.

Snyder has reported a series of 110 cases, in which a relatively small dosage—5 to 10 million organisms—was employed, with excellent results. Snyder considers the method more satisfactory than any other at present available. No kidney injury was observed following the injections.

Pemberton treated 19 cases of arthritis with intravenous injections of typhoid vaccine—using 25 million organisms of the U. S. Army

vaccine. Of this group 7 definitely improved (36%) and in two the results were uncertain; in the rest there was no change, although one of the patients was apparently made worse. In more than half of the patients the temperature rose to a more or less uniform height—103° to 104° F.

Pemberton, working with military cases, calls attention to the fact that many of these soldiers had received repeated injections of typhoid vaccine subcutaneously without effect whatsoever on the arthritic disability, while the intravenous injection, which seems to stimulate the catabolic processes of the body as a whole, may after a single injection, produce evident clinical improvement.

Harding also treated a number of cases (17) while in military service, but reports that his results were not satisfactory.

Cross treated 14 cases with typhoid vaccine, using an intravenous dose of from 25 to 250 million organisms. The results were quite satisfactory, most of the cases clearing up very promptly; there were no ill effects and no endocarditis was observed following in the course of the disease. While he observed a leukocytosis following the injections he does not consider this the sole factor in the cure of the arthritis. According to his experience "with larger doses and greater severity of the chill the patient has experienced greater and quicker relief than with small doses" this coinciding with the experience that other observers have had in arthritis.

Cadbury treated 27 cases of arthritis of varied etiology with intravenous injections of typhoid vaccine. The results were as follows:

4 acute arthritis (uncomplicated) cured.	
1 rheumatism with cardiac complications and sepsis—improved.	
16 chronic arthritis	{ 2 cured
	{ 7 markedly improved
	{ 7 slightly improved
5 gonorrhoeal arthritis	{ 1 cured
	{ 4 improved
1 luetic	improved

Gow has also published his experience with nonspecific therapy, using either proteoses or heterovaccines, and concludes that in certain forms of arthritis great benefit has been derived from intravenous protein therapy. Vaccine is given entirely for a shock effect. The type of joint disease which responds best, in Gow's experience, is the multiple infective arthritis for which no active source of primary infection or septic absorption is demonstrable. While Gow regards intravenous protein therapy as of great value in certain carefully selected cases—more particularly of arthritis, the septicemias and coliform infections—he states most emphatically that it is not a panacea for all ills; and even in those diseases in which it is of use it is to be regarded solely as an accessory weapon to be employed

in conjunction with, not to the displacement of, other remedies.

Cowie and Calhoun have made a very detailed and careful study of a small series of arthritic cases that had proved intractable to other forms of therapy, including 2 cases of chronic multiple peri-arthritis deformans; one each of hypertrophic arthritis deformans, chronic multiple peri-arthritis deformans, atrophic arthritis and hypertrophic spinal arthritis; two of acute rheumatism; two other cases were treated, one a gonorrhoeal vulvovaginitis and the other a suppurative mastoiditis, complicated by chronic pulmonary tuberculosis. Typhoid vaccine in relatively large dosage—1 billion organisms—was used to give the reaction, which was in some instances quite severe. Under the vaccine treatment most of the arthritic cases made noticeable improvement, although it was not to be expected that pathological alterations which had become chronic would be perceptibly changed or modified. The case of vulvovaginitis was not completely cured despite several injections. The chronic suppuration of the ear was completely cured after the second injection. In a recent paper Cowie has briefly reviewed his experience with protein therapy. He finds it most useful in acute and subacute arthritis.

Boyd has also employed typhoid vaccine, using it in a relatively moderate dosage (50 million) with success in a variety of diseases originating in focal infection, including arthritis.

In the European literature one finds numerous observations concerning the use of nonspecific therapy in arthritis. Typhoid vaccine has been employed less frequently, but milk injections, following the original recommendation of Müller and Weiss, have been commonly used. (Edelmann, Panczyscyn, etc.) Colloidal metals have also found favor, while Edelmann found that a combined form of therapy—using salicylates and milk injections—gave results that practically assured success in every case.

Voigt, Moewes, Voigt and Corinth (iodid-silver colloid), Mukerjee (colloidal sulphur and mercury), Reichmann (colloidal silver), report on arthritis treated with the intravenous injection of colloidal metals.

Zimmer used casein injections both intravenously and intramuscularly, the dose varying from 1 to 5 c.c. of a 5% solution. He reports on 150 ambulatory cases treated in the Polyclinic and some 30 cases treated in private practice. The cases included arthritis deformans, old rheumatic and traumatic arthritides as well as a number of other origin. His general experience led him to the belief that the most desirable results were obtained when the injections elicited a strong focal reaction with a relatively mild general reaction.

His cases of subacute arthritis and gonorrhoeal arthritis were either cured or markedly improved. The immobility incident to the older gonorrhoeal involvements was not altered.

In arthritis deformans there resulted a definite improvement in mobility as well as a lessening of the pain.

*Gout.*—In these cases a focal reaction of considerable extent was precipitated with prompt resorption.

In several cases of neuritis there was prompt improvement.

The use of the cartilage extract of Heilner—"sanarthrit," in chronic arthropathies has been reported upon by Umber and Meyer and also by Reinhart, by Sonntag and by Lämpe. Umber reported satisfactory results in patients and Meyer has made some experimental studies on arthritis in animals. Reinhart treated 23 cases of chronic arthritis in whom the pathological alterations had in some instances been of very long standing, with decided bony changes visible on Roentgen examination. In 22% of these cases there was almost complete cure, some of the patients who had been bedridden for long periods of time being able to be up and about after two or three injections, and the improvement was permanent. In 48% there was some improvement, part of this being permanent also. The other cases, despite repeated injections showed no improvement whatsoever.

There was no doubt in Reinhart's mind that the effect of the "sanarthrit" was due solely to the nonspecific reaction that followed the injections.

Roos in his recent discussion of the treatment of arthritis discusses the use of sanarthrit and reports one case so treated.

Stern has treated some 25 cases of arthritis with Heilner's sanarthrit of whom 10 showed no improvement. In 4 cases the condition was made worse, in only 8 was there some evidence of improvement, and this was usually a subjective finding. Denecke has compared the effects of sanarthrit and casein injections in 30 cases. The milk, casein and "gonargin" injections resulted in less focal reaction and he does not consider the effects quite like those obtained with sanarthrit.

**Discussion.**—The treatment of acute arthritis has offered one of the most attractive fields of therapy for nonspecific procedures and the results have in general been very satisfactory. In perhaps 40% of the cases one or two injections completely terminate the disease, in another 30% the improvement is marked and recovery made complete on further injections, while in the balance there may be either a transient improvement with a relapse later, or no marked clinical improvement. It is true that the methods as so far employed are not pleasant for the patient—typhoid vaccines, or vaccines of any kind in sufficient dosage to cause a severe reaction; proteoses, or milk, are all followed by a chill, headache, a sharp febrile temperature reaction, occasionally nausea and a general feeling of malaise. And yet the general clinical experience has been that a sharp general re-

action is followed by the best clinical results. Of course, efforts have been made to inject substances that would give the same therapeutic effect without the severe reaction. Brooks and Stanton have, for instance, used the lower fractions of digestion products obtained from ox fibrin for injections in arthritis. With this product they claim to have obtained satisfactory clinical results with practically no unpleasant systemic reaction on the part of the patient. The dosage of these lower split products was about 12 milligrams for intramuscular injection, while one-fourth or one-third of this dose was given for intravenous injection. They observed improvement in all of the 8 cases of arthritis treated with this preparation.

Their experience differs from that of the majority of the clinical observers in their ability to obtain therapeutic results without marked general reaction. It has been our experience in treating arthritis that unless a sharp reaction was elicited at the first injection, subsequent injections would as a rule be followed by little or no clinical improvement. We have felt that arthritis was one of the diseases where such a sharp reaction was justified and where typhoid vaccine, toxic though it is, seems to give the most brilliant results. Usually the arthritic patient is an excellent risk, is not very toxic, and has few contra-indications, so that a more or less heroic method of therapy is entailed with less danger than in other forms of disease.

Apart from the immediate cure of the disease another factor of importance enters into consideration when we deal with arthritis, namely the carditis that so often complicates the picture. Nonspecific therapy seems to have little or no influence on an endocarditic process once it is established unless small doses are given over a long period of time; even then its absolute value is not certain. Single large doses may at times influence the temperature of such cases for a day or two, but not, as a rule, over a longer period of time (Kinsella). It is probable, however, that the early termination of the arthritic process by nonspecific therapy does prevent the establishment of endocarditis in a definite number of cases and in the prevention, rather than the cure of endocarditis, this form of therapy perhaps offers a valuable aid.

From the point of view of the hospital management of arthritic cases another factor of importance must be emphasized, namely, the relative cost of maintenance of the arthritic case. If by any form of therapy the period of hospitalization can be shortened from the average of 5 or 6 weeks to a period of a week or two, its usefulness from an economic standpoint will be apparent.

Possibly an unbiased review of the subject, such as that recently published by Torrey, will be of greater value than my personal impression, which perhaps may be prejudiced in favor of this form of treatment.

Torrey first recalls the rather interesting work of Terc, who treated a large number of rheumatic cases with bee stings, following which the patient often reacted with a typical general reaction—fever, general malaise, etc. When the sting was repeated over a period of time the patient became more or less refractory and during this refractory period the symptoms of the arthritis disappeared. Langer later repeated this work, using an extract of the bee poison, but his clinical observations were not so extensive nor so conclusive as those of Terc. More recently Dold has investigated the poison of the bee and has tried to sensitize animals to the bee toxin, but without result. Torrey then continues: "The lack of result with sera and vaccines, unless the administration is followed by a definite febrile reaction, and the good result following such reaction, no matter what agent is used, indicates that a nonspecific agent alters bodily conditions materially. It is not clear whether actual infection is influenced by allergic or anaphylactic reaction. More reason exists for the view that the change affects the toxic expression of the infection, and that, while the organisms are still retained in viable form, their presence, or products, do not excite response by marked tissue change. There is probably a prompt detoxicating action exerted in the blood or tissues by the allergic response to the introduction into the blood stream of a foreign protein. While a similar response may be elicited to a less degree by subcutaneous or intramuscular injection of toxic proteins the sudden and full effect is attained only by intravenous injection where the protein is put into the blood unmodified by passage through other tissues and unaltered by cell or membrane selection. The usual typhoid prophylactic initial dose of 500 million killed typhoid bacilli given subcutaneously seldom gives a severe reaction; if given intramuscularly there is more apt to be a more marked febrile response, while one-tenth of that dose given intravenously will as a rule promptly produce a chill and a sudden rise in temperature to 103°-105° F. (39.4°-40.6° C.). The ultimate gain in specific immunity against typhoid infection will be much greater in the former case but a detoxicating action and termination of acute inflammatory processes will follow promptly after a severe reaction to the small dose given intravenously but not after the gradual absorption of the larger subcutaneous dose.

Two questions suggest themselves: (a) While experience offers abundant evidence that arthritis can be promptly terminated by such intravenous therapy, is it a safe procedure and does it for this purpose show any decided advantages over salicylate therapy? (b) Granting that arthritis may be controlled by this means, is there any indication that carditis is prevented or favorably influenced?

(a) Regarding the safety of the procedure. Bacterial extracts or emulsions vary so greatly in their toxic effects that great care must be used in the selection of the strain and the estimation of the dose.

As Miller states, it is necessary always to start with a minimum dose of vaccine until its toxic index has been gauged. The writer has heard of a fatality resulting from the intravenous use of typhoid bacilli. The reaction is so severe that it would, offhand, appear that the margin of safety was a narrow one. On the other hand long series of cases so treated have been reported by Miller and Lusk, by Cecil and other American observers.

As for the use of unknown quantities of mixed organisms with no means of duplicating surely the strains used, it would seem extremely hazardous to use such products intravenously; and where such severe reactions are concerned, very difficult in any event to judge dosage.

It would appear safer to use a definite compound as suggested by Jobling (proteoses) where the dose can be accurately determined by weight and where stability can be assured.

The writer has used formaldehyd intravenously to accomplish the same reaction. The toxic agent introduced here is probably a combination of formaldehyd and serum protein. The systemic results are similar to those accomplished by the bacterial injection. Two years ago the writer with his resident physicians at the Philadelphia General Hospital treated 29 cases of acute and chronic arthritis by this method. In these cases careful search was made for signs of renal changes, blood breakdown or other signs of renal damage but we could find no evident bad effects.

It might be said that while bad results have not been shown to follow careful intravenous therapeutic measures we are dealing with a most potent agent and the safety of this procedure has not been assured. It is probably not justifiable to employ this method of treatment routinely unless more is to be accomplished than simple relief of the arthritis. In most cases salicylates and good nursing will accomplish this result in a few days' time.

(b) As regards the second query, Is the development of carditis prevented or favorably influenced by this form of treatment? a much larger collection of cases will be necessary before this question can be answered. It is said that established active endocarditis is not eradicated; further, that when endocarditis is present arthritis tends to recur after intravenous treatment, showing that the infection remains.

The writer has not used intravenous therapy in cases with severe endocarditis or in those showing evidence of severe myocardial degeneration. The patients were selected as a rule among younger adults either refractory to salicylates or showing a very severe degree of arthritis, or those who, having observed results in other patients, requested this form of treatment. These patients were usually laborers from railroad construction gangs or workers in munition plants and it has been impossible to follow up these cases properly, but

it must be said that at the time of leaving the hospital none of them showed any serious cardiac damage. We endeavored to keep all rheumatic patients in bed for three weeks after the temperature reached normal and succeeded in most cases in doing so.

Any measure that will protect against carditis will be of tremendous importance and while in this case we may be merely clutching at a straw the subject should be studied carefully. It is recognized that infection is prone to implant itself upon the heart in which there has been tissue damage and it is more than possible that endocardial damage results first as a toxic expression, as it may in the joints, and that the liability of a permanent infection may be reduced by the detoxicating action of the allergic response. The writer's feeling is that serious cardiac trouble is less apt to develop when this form of therapy is used. Realizing the risk attendant on its use he is still inclined to try it on young and vigorous individuals where the myocardium is not greatly damaged."

This conservative résumé of Torrey's is quoted in full because of its dispassionate and critical perspective and because it emphasizes several points that should be kept in mind—whether it is a dangerous method of therapy; if not, is it a better method than our present one, and finally, does it prevent cardiac complications?

While we by no means believe that the goal in therapy has been reached when we inject typhoid vaccine intravenously—other agents may be much better and may be much less uncomfortable for the patient—yet we have never seen any ill effects from moderate doses of typhoid vaccine injected intravenously when reasonable care was exercised to exclude alcoholics and severe heart cases. It is considered safe enough to enable one hospital to make the injection a routine procedure for all rheumatic cases entering the service.

Our present expectant therapy or salicylate therapy fails in a definite percentage of cases. In a good number it is temporarily effective and is followed by a relapse. In others cardiac complications are superimposed even during the course of the salicylate treatment. It is furthermore a protracted therapy and therefore an expensive one.

Nonspecific therapy does frequently effect improvement and cure of the disease where salicylates have been used without avail. Usually one or two injections will disclose whether or not we can expect much relief by the nonspecific agent and when it is effective, it is rapidly so. My own impression is that it materially lessens the number of cardiac complications, although I cannot present definite statistics to that end. And in terminating the disease abruptly we lessen the number of chronic arthritic cases, which, once established, are so intractable to treatment.

To the clinician who is satisfied with his present method of treat-

ment of acute articular rheumatism, or of chronic arthritis, nonspecific therapy naturally has nothing to offer. To those of us who are not so satisfied I believe it adds a definitely useful agent and at times a very powerful one. Indeed to those who are interested in nonspecific therapy or the mechanism involved, the arthritic cases offer a particularly valuable field for research. There is practically no risk to the patient—as there might be in more or less experimental work on the more acutely ill—the signs of improvement or retrogression are objectively under the control of the physician and the interesting focal reaction elicited by the nonspecific agents at the inflammatory site can be carefully observed, especially in the more chronic type of arthritis.

The mechanism that is involved in the recovery of the patient is still quite obscure. It is to be taken for granted that we must first of all seek to remove any apparent focus of infection. Whether the joint pathology always represents actual bacterial invasion or at times merely a focal reaction of hypersensitive tissues is by no means a settled question. We do know that the nonspecific injection brings about a focal reaction and that the mechanism of recovery hinges on this reaction. Whether, as a result of the reaction the local tissues become immune to the toxic effect of bacteria still alive in the focus, whether it means merely an increased tolerance to toxic split products set free at a distance and to which the local tissues had heretofore been sensitive, or whether we deal with the actual destruction of bacteria which had become localized in the joint is not determined. We can simply point to the analogy that exists between the skin and the joint tissues in their property of distinct local sensitization, and to the fact that the reaction, being a focal one (a Herd reaktion), can be brought about by a great variety of agents and metabolic alterations (the recent paper of Gaisbeck on acute arthritis and hemiplegia is of interest in this connection); and as such is typical in its manifestations both in the negative phase (increased inflammation) and the positive phase (decreased inflammation). For the therapist it is the latter that is of greatest interest.

## CHAPTER IX

### THE TREATMENT OF TYPHOID AND PARATYPHOID FEVER

Investigations in the treatment of typhoid fever formed the basis upon which our modern conception of the nonspecific factors in therapy are based, not only in the very recent contributions to the literature, but in the older work such as that of Rumpf.

**Typhoid Vaccine.**—In the decade preceding the war the therapeutic use of typhoid vaccines in typhoid fever had been developed particularly by French scientists (Chantemesse and Widal, Vincent, etc.) and a number of vaccines were elaborated by them, each with some supposed point of superiority. The sensitized vaccine of Besredka had been used with a measure of success. Stern many years ago had suggested the use of an antitoxic agent, while the use of convalescent serum was introduced by Hammerschlag and used also by Königfeld, von Jaksch and Pollak. A comprehensive review of this period and of vaccine therapy in typhoid fever in general will be found in Gay's monograph, as well as in the report of Krumbhaar and Richardson. The latter reached the conclusion that the larger the dose of vaccine, the better the therapeutic result. But large doses of vaccine were not in vogue; one hesitated in giving large reactive doses in chronic diseases where there was little risk; naturally enough this caution was more than observed in such an acute condition as typhoid fever where logically it would seem to be decidedly unwarranted to add more toxin to an already overburdened organism.

**Intravenous Injections.**—From two quite independent sources, however, this established view was rather abruptly overthrown. In Argentine a group of clinicians found that if they injected typhoid vaccine intravenously during the course of typhoid fever certain remarkable critical terminations of the disease were to be observed; in other cases the disease terminated by lysis shortly after the injection; even those that were not affected in so far as the temperature course was concerned seemed much less toxic than before the injection. This work, carried out by Penna, Torres, Dessy, Grafiolo, Fossati and others, formed the basis on which Kraus later began his work with heterovaccination in typhoid fever.

At about the same time Ichikawa published a series of cases of typhoid fever treated with intravenous injections of typhoid vaccine with similarly striking results. He used a sensitized vaccine for the

purpose, made up as follows: 10 loops of fresh typhoid culture were suspended in 10 c.c. of human typhoid convalescent serum and incubated for 5 or 6 hours. The organisms were then centrifuged from the serum, washed three times in physiological salt solution, suspended in 100 c.c. of physiological salt solution with 0.3% phenol and finally shaken for 1 hour. The vaccine was not heated. Of this emulsion 0.5 c.c. was diluted in a syringe of saline before injection and the whole slowly injected intravenously.

In most of Ichikawa's cases a single injection sufficed to terminate the febrile course of the disease; in some the result was not quite so marked. After the critical drop in the temperature the temperature would again rise in these cases, usually remaining intermittent in type and much lower than before. The general condition of these latter patients was always much better after than before the injection. In the refractory cases the injection was usually repeated once and even twice until the desired result was obtained.

Ichikawa assumed that the effect on the temperature curve was due to a mobilization of antibodies that had been formed in the cells during the course of the infection but had not been thrown into the general circulation until the vaccine was injected intravenously.

The mortality in this first series was 11%, rather high in itself, but not in comparison to the death rate in untreated cases in the Osaka Hospital, which was around 30%.

Ichikawa did not observe any ill effects from the vaccine injection; indeed he considers it unjustifiable to neglect the advantages of intravenous therapy merely because certain inherent dangers are, theoretically, to be considered. He watched particularly for cardiovascular changes but did not have any collapse cases, and hemorrhages were less frequent in his vaccinated cases than in the untreated. In a few cases he did observe hemorrhages from 1 to 3 days after the injections; usually they were slight and not alarming in character. In two cases he observed hemoptysis, twice nose-bleeding, and in two cases hemorrhages into the skin, but they were all mild in character and did not recur. The reaction that occurred—chill, fever to 40° C., relatively high pulse, occasional nausea, dyspnea, etc.—was transient; even the increased temperature never persisted over 24 hours.

**Heterovaccines.**—Kraus and Mazza reported their work in 1914 in which not only the results obtained with intravenous injection of typhoid vaccine in typhoid fever was described, but the use of heterovaccines was taken up. Ichikawa had previously noticed that with typhoid vaccine he could treat paratyphoid fever just as well as typhoid. Kraus and Mazza found that colon vaccine did just as well, and besides reported on the effect of the intravenous injection of such vaccines in puerperal infection, where relatively long standing infections were promptly terminated and the disease process

cured. Kraus suggested the extension of the method of treatment to a number of diseases such as scarlet fever, plague, septicemia, etc.

Other reports were soon published dealing with nonspecific therapy in typhoid fever; most of the observers first used typhoid vaccine. Thus Rhein tried it in 33 cases. He prepared his vaccine as follows: To 5 c.c. of Halle typhoid vaccine and 0.5 gm. pure phenol, physiological salt solution was added to a volume of 100 c.c. Of this preparation he employed 0.6 to 1.4 c.c. diluted with 8 c.c. physiological salt solution for intravenous injection. Within one to two and a half hours a rise in temperature and a chill of varying severity and duration (five to thirty minutes) occurred in 94 per cent. of the cases. Injections were made only in patients in whom the diagnosis was clear clinically or bacteriologically. Three of the patients treated showed paratyphoid bacilli A in the blood. Patients exhibiting the steplike curve of defervescence were excluded, as were also those suffering with complications such as pneumonia, pleurisy, nephritis, or myocarditis. Status typhosus, with delirium and bronchitis, but with good pulse, was not looked upon as contra-indication for injection of vaccine. Thirty-three patients received the injections and 6 of these had a second injection. In 9 cases there was a critical fall of temperature within one day after the first injection and in 1 case after the second. In 13 cases a favorable effect on the temperature curve was noted after the first injection and in 3 cases after the second injection. In 8 patients there was no effort whatever on the temperature curve, and in 2 of these a second injection was also without visible effect. On the other hand, 3 patients who were unaffected by the first injection reacted favorably after the second. In the 3 cases of paratyphoid fever a critical fall of temperature was not observed, but there was a gradual lowering in the fever. Of the patients injected, 3 died; in none could the death be attributed to the injection. Of all the patients treated, only 1 suffered from intestinal hemorrhage, which occurred six days after the injection. Other complications were not observed in the injected patients. No evidence of collapse even in patients with weak pulse was seen. The reaction of the patient to the injection was studied with relation to the following clinical signs or symptoms: Bronchitis, palpable spleen, roseola, diazo-reaction, leukocyte count, eosinophil count, and bacteriemia. A favorable response to the injection could not be correlated with any of these. However, after crisis, comparatively many eosinophils (100 to 200 per c.mm.) appeared in the blood in twenty-four hours in spite of the leukopenia, and the diazo test remained positive as long as three days after the temperature was normal. It was noticeable that with larger dosage (4 c.c.) the crisis was of shorter duration. Since no ill effects followed the injection, and, on the contrary, in 48 per cent. of the cases the fever was shortened and in 30 per cent. cure followed within two days, Rhein believed

that in every case of uncomplicated typhoid fever, bacteriotherapy should be tried.

Biedl and Eggreth also gave their experiences with the vaccine treatment of typhoid fever. Biedl treated a series of 22 cases of severe typhoid fever in the beginning of the second week; the blood culture was positive in all of these. Of this number 2 are excluded. Both were men with high fever, status typhosus, and recurring epistaxis, the last nose-bleed occurring one day before in each case. Two hours after injection of the vaccine there occurred in each patient an uncontrollable hemorrhage from the nose which led to death. Of the remaining 20 cases, 11 received Vincent's vaccine (typhoid bacilli killed with ether), first 100 million, later 250 million to 300 million in 2 c.c. of salt solution, and 9 were treated with Besredka's vaccine intravenously (sensitized living typhoid bacilli) in doses of 250 million to 300 million in 2 c.c. of salt solution. The end result was as follows: Of the cases treated with Vincent's vaccine 3 died; 2 received subcutaneous injections and died fourteen and eighteen days respectively after the injection; 1 treated intravenously, after an initial favorable response, died in the third week from severe bronchopneumonia and heart weakness. Evidently none of these deaths were due to the vaccine. The remaining 8 patients recovered. All of the patients treated with Besredka's vaccine recovered. Biedl's impressions were decidedly favorable. After intravenous injection the temperature rose in one to two or three hours from 39° to 40° C. (102.2° to 104° F.), in one case even to 42° C. (107.6° F.), followed in twelve to eighteen hours by a critical fall of temperature to normal. No signs of collapse were observed; indeed, in two cases the injection was made when the patients were in a state of collapse with a pulse which could not be counted. Within three hours the temperature rose, the pulse became much fuller with a rate of 100 per minute. Following crisis the patients felt much better. The patients treated with Besredka's vaccine remained afebrile. Some of the other patients had slight evening elevations of temperature; in none above 38° C. (100.4° F.). Eggreth treated a series of 43 cases of typhoid with a single intravenous injection of 0.5 to 1.0 c.c. of Besredka's vaccine. Subcutaneous injections had produced no result. In 34 cases of Eggreth's series a critical fall of temperature followed within three to twelve hours after the injection, frequently with profuse sweating and marked relief of headache and delirium. Of these patients 31 remained afebrile; the remaining 3 developed fever after twelve, fourteen, and fifteen days, due respectively to endocarditis, to bilateral purulent parotitis, and to suppurative osteoperiostitis. The majority of the patients received the injection between the seventh and sixteenth day of the disease. In a group of 8 cases in the fourth and fifth week of the disease, suffering with broncho- or pleuropneumonia, the injection was ineffective. The forty-third case died

three hours after the injection. An autopsy was performed which revealed typical typhoid lesions in the small intestine, pneumonia, and myocarditis. The patient had been brought to the hospital unconscious and desperately ill, and a poor risk. Paltauf, at whose request Biedl and Eggreth had reported their experiences from the military hospitals, uttered a word of warning, as he had heard of a few instances of collapse following the intravenous use of Besredka's vaccine.

In the earlier experience collapse and even death after the intravenous injection of relatively large doses of typhoid and other toxic vaccines was not uncommon (Kraus and Mazza, Boral, v. Reuss) and the caution expressed by Paltauf is more than justified. The early doses were tremendous and would put even a healthy individual to considerable strain; that patients severely ill would occasionally succumb to the treatment was therefore not unexpected.

At a meeting of the Gesellschaft für Aerzte in Wien (June 18, 1915) a number of clinical reports were presented which are of interest. Nobel treated 14 cases of typhoid with intravenous typhoid vaccine injections. Of these 11 were cured after one injection, 3 died. Zupnik, who used typhoid, meningococcus and albumose injections, brought out the fact that small doses were much preferable to the larger ones heretofore used, because the therapeutic result was just as good and the danger to the patient much less. Fleckseder treated 41 cases of typhoid with intravenous injections of Besredka vaccine. Of these 21 cases proved refractory. In 20 cases the temperature came down after several injections. He used fairly large doses and saw several cases of vasomotor collapse. In two cases a hemorrhagic nephritis developed. He therefore considered the treatment of doubtful value, particularly in severe cases. Stoerk used albumoses and obtained results that were similar to those obtained with typhoid vaccine.

Meyer reported a series of cases treated with typhoid vaccine with typical results but in a later discussion is rather inclined to think that the intravenous injection of typhoid vaccine is too strenuous. He has come to the conclusion that some of the milder agents will be found much more satisfactory for general use. Lucksch has reached the same conclusion. Other earlier reports are those of v. Cзылharz, v. Cзылharz and Neustadtl, Neustadtl, Reibmayr and Decastello, Sladek and Kotlowsky.

Reibmayr and also Decastello reported on a series of cases treated with cholera and colon vaccines. In Decastello's cases he injected 30 million organisms (colon) which gave a sharp reaction. In 10 cases of typhoid fever 4 responded by defervescence by crisis, 1 by lysis after the first injection. Three more cases became normal by lysis after the third injection; in two cases there was no effect

to be observed on the course of the disease following the injection.

Thus heterovaccine therapy was, clinically at least, definitely established and has come to be accepted even when the vaccine is used subcutaneously. Stein in presenting the results on about 1,500 cases of typhoid treated by him both subcutaneously and intravenously found that by either method of administration colon vaccine would give comparable results.

The theory could still be advanced that the vaccines injected were more or less related biologically and that group reactions might immunologically account for the result, an idea that Ichikawa had advanced to account for the success of the typhoid vaccine in paratyphoid fever.

**Milk and Albumoses.**—Even this last resource of our older conception was swept away with the demonstration of the fact that typhoid fever could be treated with equally good clinical results with intramuscular injections of milk or intravenous injections of protein products.

Lüdke in 1915 reported on 23 cases of typhoid fever treated with intravenous injections of deutero-albumose and later reported on a series of 78 cases of typhoid fever and paratyphoid B fever with the following results:

In 26 cases there was a complete, critical defervescence.

In 10 cases there was a complete defervescence in from 3 to 5 days.

In 31 cases the temperature came to normal in from 7 to 12 days, while in 11 cases there was no appreciable effect on the temperature curve.

The deutero-albumose used by Lüdke contained about 15% of salt as well as some protalbumose and was used in the majority of cases in 10% solution. In the normal individual the injection of 1 to 1½ c.c. of this solution caused no reaction. (In one normal individual a second injection given after an interval of two weeks produced a slight chill and a rise in temperature that persisted for about 4 hours.)

Lüdke has never seen an unfavorable effect on the pulse following proteose injections in any acute infection. There were no deaths in these 78 cases of typhoid or paratyphoid fever. The average duration of the disease in these cases was from one to two weeks and he has noted, as others have constantly reported, that the earlier the treatment is inaugurated, the better the results.

Perhaps the largest series treated with deutero-albumoses is that of Holler (350 cases). His method of injection differed materially from those heretofore employed in that he gave daily injections, usually commencing with 1 c.c. of a 10% solution and increasing the dose about 0.5 c.c. with each injection, depending of course on the reaction. His cases were all kept on a fluid diet, were given charcoal as well as urotropin, but otherwise had no medication apart

from the proteose injections. His mortality was only  $\frac{1}{2}$  per cent.; he experienced no prostration or hemorrhage of moment in the entire series. The average duration of the disease was 10 days. Naturally the earlier the cases came to treatment, the more apparent and satisfactory were the results. During the course of his experience he used ovalbumin, adrenalin, typhoid convalescent serum, horse serum and pleural exudate intravenously, but for general use he obtained the most satisfactory results with the proteose.

Jobling and the writer treated a series of typhoid cases with a secondary proteose preparation, some of which were reported in a paper published in 1916, and Miller and Lusk, and Miller reported on the treatment of typhoid fever both with typhoid vaccine, with proteoses and with pollen extract. Nolf has also used peptone in typhoid fever with satisfactory results.

In 1916 Schmidt, Luithlen, Saxl, Bruck and Kiralihyda, Müller and Weiss, introduced intramuscular milk injections. Two factors tended to popularize this agent—the relative ease of administration (intravenous injections being at times more or less formidable) and the availability of milk—so that for the past three years one finds perhaps most of the reports on the effects of nonspecific therapy based on experience gained with milk injections. Saxl, Bruck and Kiralihyda at first reported on the use of milk on gonorrhoeal complications, but Saxl shortly reported on 26 cases of typhoid fever treated with injections of this kind. In almost all cases, after an initial temperature increase that persisted for about two days, the temperature came to a normal level by lysis. Corinaldesi gave intravenous injections of 1 c.c. of a 2 or 4 per cent. solution of deuterio-albumose in a case of typhoid and one of paratyphoid, according to Lüdke's technic. No benefit was apparent. Then he tried intramuscular injections of 5 or 10 c.c. of sterilized milk in five patients with lobar or bronchopneumonia or typhoid and was astonished at the prompt and permanent improvement that followed one, two or three injections, without disturbances or much local reaction. There was only rarely a slight chill and it was mild. His findings thus confirm the way in which parenteral introduction of some protein substance is able to stimulate the defensive forces and aid in the throwing off of the disease, irrespective of the nature of the protein injected.

Galambos made an effort to determine which of these agents so far described might be of greatest value. In a series of 136 cases he used deuterio-albumose, vaccines (colon, gonococcus and staphylococcus) and salt solution. In 25 cases treated with injections of 1 c.c. of a 4% solution of deuterio-albumose he obtained a critical drop in the temperature in 50% of the cases. Vaccines seemed much less effective; more and repeated injections had to be given in order to obtain the same result. The dosage varied, about 25 million of colon

and gonococcus organisms were injected, 250 million of the staphylococcus, in order to obtain a satisfactory reaction.

When 100 c.c. of physiological salt solution was injected a defervescence was obtained in 70% of the cases.

In the total series the mortality was 6% and the results can be summarized as follows:

Critical defervescence .....	22%
Prompt lysis .....	22%
Marked improvement .....	18%
Moderate improvement .....	9%
No effect .....	28%

As a result of his investigation Galambos inclined to the treatment with protein split products.

The treatment by salt solution injections was first reported by Engländer. Engländer while treating a bleeding typhoid case injected about 300 c.c. of salt solution intravenously and found that this was followed by a typical chill and a defervescence the following day. Mitlander later reported on the same method.

**Comparative Results.**—Galambos—who studied the intravenous therapy of typhoid and paratyphoid fevers with Besredka's vaccine and with albumose, heterovaccines and salt solution, as just mentioned—reported later on the treatment of 120 cases with methylene blue.

He considers intravenous treatment limited in its application for several reasons: it requires a certain degree of skill and experience on the part of the physician, who must rule out contra-indicated cases—myocarditis, pneumonic complications, etc.; there are associated with the injections certain dangers of hemorrhage and of collapse (from 1% to 2%); the substances used are not chemically defined and experience must be gained with the dosage before one can be fairly safe in using the method. This came to Galambos' attention when he reviewed his earlier and his later results with nonspecific therapy. In his last 50 cases where he used only a small dose of Besredka vaccine intravenously ( $\frac{1}{4}$  c.c.) he had no hemorrhage or collapse at all, and he likewise had no ill effects in his series of 60 cases treated with albumoses. The intravenous injection of larger amounts of salt solution was found too cumbersome for routine use.

To overcome some of these practical objections he began the use of methylene blue, which, being a chemically defined substance, could be standardized, and while, being a protoplasmic stimulant as the others, could be given by mouth without a marked reaction. He gave 1.2 gm. per day in doses of 20 cgm. every 4 hours. The effect on the temperature was usually apparent in a few days, usually declining by lysis. The euphoria so commonly observed in nonspecific therapy was apparent in most instances. The medication was continued some days after the temperature reached normal. If discontinued too early an occasional recrudescence was noted.

In 120 cases so treated the severity of the disease was roughly as follows (50 cases of mild disease were not treated at all):

63 moderately severe; typhoid 2; Para "A" 35; Para "B" 4; undetermined 22  
 23 severe; " 5; " 11; " 1; " 6  
 9 very severe; " 2; " 4; " 1; " 2

Of the typhoid cases many had had a prophylactic injection shortly before their admission to the ward. (There was probably no vaccination against paratyphoid, although it is not specifically stated in Galambos' paper.)

The results of the methylene blue therapy was as follows:

- In 13% lysis set in immediately after the treatment.
- 26% lysis somewhat more delayed.
- 13% favorably influenced, but not much effect on temperature.
- 44.6% not influenced.
- 3.4% died.

Compared to the results with the vaccine therapy before used the mortality was somewhat less but the general effect on either critical or lytic termination of the disease not so apparent.

When one comes to study the comparative value of the intravenous method of therapy as contrasted with the subcutaneous injection of vaccine in the treatment of typhoid fever, the statistics of Barrenscheen are of value.

Barrenscheen treated over 200 cases of typhoid, using Besredka's vaccine intravenously as well as subcutaneously; a small series was also treated with the Vincent vaccine subcutaneously.

	Cured	Unfavorably Infl.	Not Infl.	Died
Besredka Intravenously				
136 cases .....	87 = 63%	5 = 3.6%	34 = 25%	10 = 7.35%
Besredka Subcutaneously				
52 cases .....	26 = 50%	3 = 5.7%	17 = 32%	6 = 11%
Vincent Subcutaneously				
19 cases .....	4 = 21%	3 = 15%	12 = 63%	0 = 0

The intravenous dose was 100 million (sensitized vaccine) and if the patient was not afebrile after the first injection a second dose was given after two or three days; no more than three doses were given, because Barrenscheen found that if the patient was refractory it was useless to continue. In 30% of the cases a critical termination of the disease was obtained after a single injection.

For subcutaneous injection he used 500 million organisms, followed two days later by 1,000 million if there had been no effect on the temperature. This dose was increased somewhat for the third injection but he never gave more than a total of 9,000 million organisms during the entire course of the treatment.

As a result of his experience Barrenscheen considers, as other observers

also do, that the first week or ten days of the illness offers the best time for treatment; after the third week he considers it not only valueless but dangerous (because of the danger of hemorrhage or perforation).

He does not give it in any cases where the pulse is over 100, where there is any evidence of lung complication or where a tendency to hemorrhage is present—nose-bleeding, blood in stool, etc. If these conditions are observed the mortality would be even lower than that obtained in his series, for many of his results that were unsatisfactory were the result of his earlier efforts when he was not sufficiently experienced. In only one case did he find that death was due to a complication resulting directly from the injection. This was a perforation that came to notice immediately after the injection.

In four cases a rather widespread roseola was observed shortly after the injection. It had no further significance but might disturb an inexperienced clinician.

The intravenous injection seemed much superior to the subcutaneous, not only apparent in the statistical result but because of the prompt bettering of the general condition of the patient. Headache and insomnia disappeared, the appetite improved and the mental conditions always cleared up. On the other hand this effect was never so apparent after the subcutaneous injections and there seemed no doubt in his mind that the effect of the subcutaneous dosage was bad on the pulse. Both after the Besredka, more frequently after the Vincent vaccine the ill effect on the pulse was observed and in some instances stimulants had to be generously used before the equilibrium was restored.

Following the intravenous injections the usual reaction was observed, with temperature reactions from 40° to 41° C. (104° to 105.8° F.), in one instance to 41.9° C. (106.3° F.). The pulse never went over 120 and always remained of good quality and the patient without evidence of cardiac impairment—there was no dyspnea, cyanosis, etc. After the second injection the temperature response was not as high as with the first, nor was the leukocyte count altered as much.

During convalescence the patient should be kept rigidly in bed, at least for a week after the temperature has been normal, and careful attention given the diet and the bowels. In several cases where the patient became constipated a temperature reaction was observed which lasted several days. Occasionally a pronounced bradycardia was found during convalescence. Pulse counts as low as 36 to 50 were not uncommon in these cases, while an arrhythmia was at times present. Barrenscheen is under the impression that no myocarditis was present in his cases, but the fact that he lost two cases who got up and walked around two days after their recovery by crisis might lead one to think otherwise.

Grote treated 24 cases of typhoid with milk injections with good results but came to the conclusion that the injections must be given early if they are to be effective.

Mark White has reported on the treatment with normal horse serum; E. F. Müller on the use of casein injections, both with favorable results. Ullmann treated typhoid with "Dispargin," a silver colloid; Salomon has reported favorable results in 141 cases treated

with a colloidal gold preparation and Labbe and Moussaud have also made use of the latter agent.

Svestka and Marek used "Typhin," the nucleohiston prepared from typhoid bacilli. In 60 cases so treated they grouped the clinical results as follows: In one case the temperature increased for the day following the injection, then fell and remained normal. In 14 cases remissions began, the temperature coming down with the usual remissions normally observed in the late stages of typhoid. In the balance of the cases the remissions became greater but the disease continued the usual length of time. In 21 cases 2 injections were made; in 11, 3 injections. They observed no increase in the agglutinin titer of the serum after the injections.

Neustadt and Marcovici treated 25 cases of typhoid with "Typhin" and as a routine measure gave digitalin 2 days before the injection to counteract any tendency of collapse on the part of the vascular system. In 21 cases the injection was made intravenously. In 11 of these cases there was apparent a decided influence on the disease process—in 5 of these 11 the fever terminated by crisis; 4 cases gave evidence of some alteration and apparent shortening of the course of the disease; 3 cases were much less toxic after the injections; 3 patients died, one in collapse. Of four cases injected intramuscularly, 2 were influenced favorably, but the effect was not as marked as with the intravenous injections.

Svestka and Marek consider that the method can be used without harm to the patient and is of decided value when given early in the disease, but they did not hesitate to give it even late in the disease if the cardiovascular tone was good. They consider the state of the circulatory apparatus the chief factor in judging whether or not the patient is a suitable risk, although they excluded markedly cachectic patients as well. After the injection improvement in the general condition of the patient was apparent in practically every case.

Slaymaker reported on a few cases treated with typhoid vaccine given intravenously, the dosage varying from 25 million to 100 million. While only 9 cases were treated there were no marked results, apart from some evidence of reaction and improvement in two of the cases. One patient died. From his experience Slaymaker was not inclined to continue the use of the method. Silvestri, using milk injections, found that this treatment seemed to increase the tendency to shock and hemorrhage in the twelve cases that he observed.

In judging the relative safety or danger in the method of therapy it may be well to present briefly the statistics recently gathered by Vaughan in the American Army and others from military sources. These represent the results in vaccinated troops and may be considered quite satisfactory under military conditions.

Observer	Cases	Inoculations	Mortality Per Cent.
Bernard and Paraf .....	26	...	0.0
Hunermann .....	...	4	2.6
Hunermann .....	...	2	6.6
Crossonini .....	28	3	7.1
Crossonini .....	50	1-2	8.0
Campani and Gallotti .....	...	...	8.6
Hawn, Hopkins and Meader .....	38	...	13.1
Bonnel .....	15	3-4	13.3
Vaughan .....	270	...	11.0
Total A. E. F., 11 months .....	1242	...	13.0
H. Bourges .....	5	...	0.0
Freund .....	...	...	8.3

If we compare such a series as that of Holler (350 cases) with its mortality rate of about  $\frac{1}{2}$  of 1%, to the statistics collected by Vaughan it would seem reasonable to conclude that the nonspecific method of therapy is, with reasonable precautions, rather more satisfactory than the mere expectant treatment.

Kibler and McBride noted that the immediate effects of the intravenous injection of the typhoid vaccine, such as chill, rise and fall of temperature, leukocytosis, and changes in the concentration of agglutinin and opsonin, usually in the direction of an increase, were the same in the normal man as in the typhoid patient. Except so far as they showed that leukocytosis is rather constant after the injection of vaccine, they did not support any particular view advanced to explain the action of intravenous injection of foreign protein in infectious diseases. The number of cases observed (six), possibly too small to allow any conclusions as to the therapeutic effect of typhoid vaccine in typhoid, seemed to correspond fairly well with the results obtained in larger series.

*Bacillus carriers* have been treated with milk injections and with intravenous typhoid (para) vaccine with satisfactory results. Karrell and Luksch have employed milk, while Herz, using vaccine injections, was able to clear up 4 out of 5 patients.

**Discussion.**—A considerable number of observers have endeavored to determine whether or not there is an increase in the amount of antibodies in the serum which would account for the recovery of the patient after nonspecific therapy.

The general summary of the observations on this particular question is that while such an increase may at times be demonstrated, it is by no means a constant result of the injection and cannot therefore be identified as being the sole cause of the abortive recovery of

the patient. The agglutinin titer, which has been most often studied, is normally found to be rather high after the early stage of typhoid fever is passed and after nonspecific injections it is at times increased, at other times diminished. Nor does the increase or decrease bear any relation to the therapeutic result. Thus Rohonyi found that in some of his patients who had recovered after a single injection by a critical drop in temperature, there was no increase in the agglutinins, in opsonins or in bacteriolysin; indeed in some cases he was able to get a positive blood culture two days after the patient was clinically free from every evidence of active disease—an observation which Decastello has not been able to confirm. Lüdke was not able to determine any constant increase in the amount of agglutinins or of opsinins after his deuterio-albumose injections. Báluit observed no change in the agglutinins or the bacteriocidal antibodies, but obtained some evidence that the opsonins were increased. Svestka and Marek found no increase in agglutinins. Flechseder on the other hand claims to have observed an increase in agglutinins after albumose injections in typhoid fever.

While it is apparent that the inconstant results exclude the antibodies as sole factors in the recovery, the possibility that their sudden flooding of the lymph spaces after the permeability of the capillaries is increased following the protein shock may be a vital factor in overcoming the infection.

Whether or not cell receptors (sessile antibodies that may have increased in amount following immunization or infection without their being cast off into the general circulation) are under shock conditions mobilized and in this way increase the titer after nonspecific therapy is here a point at issue. That rabbits immunized to some specific bacterial or other protein may, on nonspecific stimulation, respond by the "shedding" of the specific antibody is an old observation. Dieudonné observed that rabbits immunized with typhoid bacilli and then injected with "Hetol" responded by an increase in the antibody production. Solomonsen and Madsen found the same true of diphtheria horses after pilocarpin injection, and Obermeier and Pick found that an injection of 5% or 10% peptone increased the agglutinin titer of rabbits immunized more than 3 months previously. Kutcher has observed that patients immunized to typhoid and cholera will show an increase in the agglutinins for dysentery (paraspecific agglutinins) and the mass immunization of large bodies of men with typhoid vaccine gave opportunity during the course of the war to observe that many varieties of shock (acute infectious diseases of various kinds, etc.) were followed by a flooding of the serum of such individuals with large amounts of agglutinins. Conradi and Bieling and also Johnson made experimental observations along the same

line, while Parlovechio found, as had Chantemesse, that the injection of nucleins increased the agglutinin and alexin titer. Ardin-Delteil, Negre and Raynaud have also reported increase of agglutinins and bactericidal substances in serum after nonspecific injections. Other procedures include the stimulation of the sympathetics (Stuber), the injection of alcohol (Friedberger), arsenic (Agazzi), salvarsan (Friedberger and Masuda), blood-letting (Friedberger and Dorner), all of which are followed by an increase in antibody titer.

It seems very probable that when the cells have become immunized during the course of the disease, a certain number of receptors are available but have not been shed. These are possibly mobilized when nonspecific injections are made.

In a previous chapter the possible mechanism that underlies the recovery in typhoid fever by means of nonspecific therapy has been fully discussed, so that it will not be necessary to again enter into the subject here.

A number of interesting questions present themselves, however, as a result of clinical observation in more recent years concerning the normal recovery from typhoid fever. In persons who have been previously sensitized or immunized the course of the disease is frequently more stormy and somewhat shortened while the difference in the mortality may not be great as contrasted with the unvaccinated. On the other hand we know that recovery can take place without the appearance of antibodies in the blood stream, as Moreschi has demonstrated in leukemia. Certainly the presence or absence of the antibodies can no longer be made responsible for the clinical course of the disease.

On the other hand the period of defervescence with its great variations in the daily temperature curve is very suggestive of the reaction of the organism to nonspecific injections. One can conceive that the daily accumulation of toxic proteins produces a summation of toxic effects with a resulting effect on the temperature curve. After the "shock" effect has passed the remission with its alteration in permeability and cellular stimulation, sets in and as the process is kept up the organism gradually becomes resistant to the intoxication until finally defervescence is complete. The study of Aller would rather confirm this conception; he presents a number of interesting examples which cannot be discussed in detail at this place. Holler's work would lead one to suspect such a basis for the normal mechanism of recovery for when he injected his proteoses in daily small doses similar temperature effects were achieved and the patient was soon completely afebrile. Lüdke has recently expressed this same view.

So, too, one can observe a variety of modifications of the temperature curve even after a single nonspecific injection. The crisis may be prompt and complete. In other cases where a continuous high

temperature has been observed, daily remissions in the temperature curve will set in after a single injection; in others the average height of the temperature curve may be altered so that from a continuous temperature of about 102° F. the temperature after the injection will have a level around 100° F., as though the heat regulation had been attuned to a new level.

The question of the mechanism of recovery brings with it the query, When is the patient cured? Does freedom from symptoms constitute cure? It has been pointed out that after the therapeutic crisis a positive blood culture may still be obtained, the spleen may still be palpable for a few days, the roseola remains a short time, the diazo reaction may persist, etc., the while the patient will be free from fever and in excellent condition. As a result of the treatment the body does not react to the typhoid bacteria. It is desensitized, not necessarily free from the infection. Very likely, though, a similar condition obtains frequently during normal recovery from typhoid fever as is evidenced by the persistence of bacteria in the bile tracts, the gastro-intestinal and urinary systems or in the isolated foci that may become manifest weeks after the clinical recovery from the febrile course. As a matter of fact Holler found no cases of carriers in his 350 cases of typhoid fever treated with proteoses, and Herz states that typhoid carriers can be freed following protein therapy. Relapses occur occasionally, but Lüdke observed that these were much milder in character and of shorter duration than in untreated cases. Bresler in his review of modern typhoid treatment brings out the fact that the small number of relapses in cases treated with non-specific injections is quite apparent and he also believes that a distinct improvement of the circulation takes place even when there has been no direct effect on the temperature.

The observation of Wiesner to the effect that the typhoid ulcers commence healing immediately after the therapeutic injection is of interest in this connection. From the therapeutic standpoint it is naturally important that the patient, even after defervescence, should be kept quiet in bed for at least ten days and longer if there is any evidence of myocardial impairment.

**Therapeutic Precautions.**—There are three chief dangers that must be kept in mind in the treatment of typhoid fever by nonspecific therapy. The first concerns intoxication. When we are dealing with a profoundly toxic patient we must be reasonably certain that he is able to bear the increase in intoxication which seemingly occurs after the nonspecific injection and which is probably due to a rapid destruction of typhoid bacteria. We have observed one such case in a profoundly intoxicated, obese typhoid patient who, despite the gravity of the risk involved, was injected with a small dose of proteoses and died within

an hour following the chill. At autopsy no lesions other than those of typhoid fever and a marked cloudy swelling of all parenchymatous tissues and a toxic myocarditis were observed.

The other two dangers are related to the gastro-intestinal tract. When nonspecific therapy is used the intestinal tract is affected to a considerable degree, depending on the severity of the reaction, the agent used, etc. There is first of all an increased motility. Coincident with it there is an engorgement of the vessels of the bowel. Both of these factors may result in an increased possibility of perforation and of hemorrhage.

Clinicians who have had largest experience with the treatment of typhoid fever state very definitely that these dangers are theoretical rather than actual. When fatalities occur following the treatment the dosage employed in producing the reaction may have been too large or the agent selected not the best one for use. The injection of both typhoid bacilli and also of proteoses is not followed by the styptic effect that we see after milk injections, and the vaccine, too, has the added disadvantage of being decidedly toxic in itself, both factors that would incline one to favor any of the other agents rather than the typhoid vaccine. The question of dosage is one that has not been definitely settled. Of course, the massive doses of typhoid bacilli that have at times been employed (1 billion and more) by American observers and which were naturally followed by disasters of various kinds should not be countenanced in typhoid fever, however well they may be tolerated in other conditions.

When typhoid vaccine is used only enough organisms should be injected to provoke a mild reaction—from 10 to 25 million—and similarly moderate doses with other bacterial vaccines. When relatively nontoxic agents are employed such as proteoses, colloidal metals, nucleins, etc., one can follow two courses. Either to give sufficient to provoke a general reaction and perhaps repeat the dose after several days if the fever has not been altered, or give small daily doses, none of which are themselves sufficient to provoke a severe reaction. Holler has used this latter method with success; it is the method that Jobling and the writer have preferred to follow when dealing with typhoid fever. The immediate results may not be quite as brilliant as when larger doses are used, but there is certainly much less danger of precipitating some decidedly grave complication. For general use we cannot too urgently emphasize these considerations.

In order to overcome some of these potential dangers, Neustadl and Marcovici usually prepared their patients, especially those that had been ill for some time and in whom there were evidences of vasomotor instability, with digitalis. Jobling and the writer tried to overcome the motor activity of the gastro-intestinal tract and the

consequent danger of hemorrhage and perforation by using opiates beforehand. There seemed to be little control, however, of the increase in peristalsis. Zupink, Müller and Leiner, Matko and Holler stimulated their cases with caffeine given before the injections.

If the pulse is over 100 and there are evidences of vasomotor instability, if the patient is profoundly toxic or cachectic, if there has been any bleeding—epistaxis, gastro-intestinal, etc., if cyanosis is present, if the disease has continued for several weeks before treatment is commenced, or if there is any evidence of pneumonic complications, it is not advisable to try nonspecific therapy. If given under such conditions the clinician must consider the dangers involved and seriously weigh the chances for collapse or hemorrhage or perforation and determine whether or not they are overbalanced by possible advantages.

#### PARATYPHOID FEVER

It will be recalled that Ichikawa treated a number of paratyphoid cases with typhoid vaccine with good results.

Holler in his series of infectious diseases treated 140 cases of paratyphoid fever with small daily injections of deuterio-albumoses. There were 7 deaths in this series.

The indications and contra-indications are those that have been discussed under the subject of typhoid fever.

## CHAPTER X

### GONORRHEA AND ITS COMPLICATIONS

The intravenous injection of vaccines in the treatment of gonorrheal complications is a procedure that antedates by a few years the more general application that we now consider under the subject of protein therapy. Bruck and Sommer had in 1912 and 1913 made use of a polyvalent gonococcus vaccine for intravenous injections in a variety of complications, such as arthritis, epididymitis and acute prostatitis, with remarkable results. Within certain limits their results paralleled the severity of the systemic response that followed on the vaccine injection. The reaction that was observed consisted of the usual rise in temperature, a leukocytosis, occasional chill and sweating, etc. It will be recalled that previously the morphological similarity of the gonococcus and the meningococcus had led Herescu and Strominger to use antimeningococcus serum therapeutically against gonococcus infections.

That fever or at any rate intercurrent infections have at times a decided effect in altering the course of a venereal infection and its complications had been noted for a number of years and had been discussed by Finger, Gohn and Schlagenhauser in 1895. In 1916 Müller and Weiss reported excellent results in gonorrheal complications with their intergluteal injections of milk and a nucleinate, similar to those of Bruck and Sommer. A number of workers at once made preliminary trials of the method in this clinical field, including Schmidt, v. Tanner, Friedländer, Elschnig, Luithlen, etc.

Smith in this country had independently come to a similar point of view in the treatment of patients suffering from gonorrheal complications in using specific sera or normal horse serum. Some of these became more or less sensitized to the serum and on further injection, responded with a decided general reaction. These patients in particular were the ones that gave the most promising clinical results, so that Smith emphasized the importance of this state of sensitization and the coincident temperature rise in the therapeutic result obtained. The experimental research reported by Arloing, Dufourt and Langeron confirms the clinical observation that it may be possible to cure certain infections by inducing an anaphylactic shock. The research was done on guinea-pigs inoculated with pyocyaneus cultures. Even a slight shock was enough to arrest the infectious process. The clinical cure was accompanied by the destruction of the germs in the blood and by the acquirement of immunity.

**Culver's Investigation of Gonorrhoeal Arthritis.**—These reports led Culver to investigate the specificity of the therapeutic procedure. He selected a series of cases suffering from gonorrhoea and some complications (arthritis, etc.); these were divided into four groups, the first of which was treated by the intravenous injection of a gonococcus vaccine, the second a similar dose of meningococci, the third of colon bacilli, the fourth of a deuterio-albumose solution. No local or general treatment other than the injections was given.

**Gonococcus Vaccine.**—In the first series Culver gave 100 million killed gonococci and repeated the dose every fourth or fifth day. The greatest number of injections given one person was 6, most of them received 5, one received but one injection. The injections were followed by a chill of variable severity coming on in 20 minutes to 1 hour and lasting 15-30 minutes. The chill was at times accompanied by headache, usually of short duration. Exceptionally, there was nausea and vomiting during the first few hours, but never severe and always transient. This occurred often in patients who had disobeyed instructions by eating heartily within a few hours of the injection.

At the onset and during the chill the patient often complained of severe pain in the affected parts (focal reaction).

Invariably the disagreeable effects of the reactions, if any appeared, disappeared in about 24 hours, and for the next 24-72 hours a variable degree of comfort was experienced. The pain and the tenderness, together with the swelling of the joints, were much improved. This prompt improvement was most likely to be of only 2-4 days' duration, and then there was a stiffness of the affected joints with some pain on motion, but usually in a much less severe form.

These relapses gradually decreased in severity following successive injections until eventually none appeared. In some instances there was no relapse, even following the first injection.

Injections were repeated on the 3rd-5th day, or usually just as the joints began to show a return to their old condition. This seems to be a more efficient method of injecting than daily injections. With daily injections, the patient is at all times having a reaction or just recovering from one. His general condition is not so good nor does the local disease respond so well.

It is usual for the severity of the reaction to decrease following repeated injections, and this decrease seemed directly proportional to the number of injections previously given.

In patients, both of whom had numerous subcutaneous injections of gonococcal vaccine, there appeared immediately following each intravenous injection a very transient reaction characterized by flushing of the face, cyanosis, dyspnea, and a tingling sensation over the surface of the whole body. These reactions lasted 1-2 minutes, after which the patients felt perfectly at ease until the usual reaction ap-

peared in 20 minutes-1 hour. This anaphylactic-like reaction may have been due to a partial sensitization from the previous subcutaneous injections. Three other patients in this series developed a mild type of a very similar condition, on the 3rd intravenous injection.

The typical temperature curve following these injections revealed a slight fall during the first part of the chill, followed by a gradual rise, which reached its maximum in 4-6 hours, and gradually fell to normal in 24 hours.

The leukocyte counts during a reaction and following were somewhat variable. Usually a mild leukocytosis just before and during the first part of the chill was observed, soon followed by a marked leukopenia, which appeared toward the end of the chill; a count as low as 2,000 being observed repeatedly during this stage of the reaction. This condition was soon followed by a gradually developing leukocytosis, reaching its maximum in 5-7 hours, and remaining moderately high for 24-30 hours. A return to normal occurred in about 48 hours.

**Meningococcus Vaccine.**—The second series of 15 patients was treated with killed meningococci in the same dose and at similar intervals as in the gonococcus series.

The reactions as far as could be determined were similar in every detail to those produced by the gonococcus vaccine. One instance of a double reaction occurred following the 1st injection, and 1 patient developed this condition after 2 injections. None of this series had had previous subcutaneous or intravenous injections.

The leukocyte curve, in general, likewise followed that of the first series very closely. One very startling difference was observed between the 2 groups. Over one-half the meningococcus series developed a more or less severe *herpes* of the lips and mucous membrane of the mouth, first appearing in 48 hours and remaining for 4-7 days. This condition did not follow any but the 1st injection, and did not become aggravated or recur when further injections were made in a susceptible person.

**Colon Bacillus Vaccine.**—This series contained but 9 patients. The reactions were in every way like those produced by meningococcus and gonococcus with the exception that the size of the dose required to produce the same results was very much less. At first a dose of 100 million organisms was given, but the reactions were so severe that 25 million were finally used as the initial dose, this to be increased if necessary to produce the desired results.

**Deutero-albumose.**—A secondary proteose made from casein was used (80 mg.) in 4% solution on a series of 4 patients, the initial dose being 2 c.c. The reaction showed some variations from those produced by bacterial suspensions, in that the chill never took place before 1 hour after the injection, and that there was no headache or

nausea following any of the injections; also the fever and leukocytosis did not reach the height produced by bacterial suspensions. Sufficient experience with this solution, however, was gained to convince one that the reaction and therapeutic effects are very similar and equally as effective as those produced by bacterial suspensions, as well as giving rise to less disagreeable reactions.

As far as therapeutic results are concerned there was no noticeable difference between the 3 bacterial suspensions or the albumose solution. To produce results therapeutically a reaction is necessary. That is, a chill must occur which is invariably followed by the temperature and leukocyte changes noted. A dose insufficient to produce a definite chill was not followed by as marked a temperature as the leukocytic reaction, and clinically there was not only no therapeutic benefit, but sometimes patients became more uncomfortable than before. The reactions following injections in non-gonorrhoeal patients were not to be distinguished from those produced in infected patients.

These observations were made by injecting a series of patients with chronic skin lesions with no history or indication of gonococcal infections. The size of the dose required to produce a reaction, the chill, temperature, and leukocytosis was alike in every way in the infected and the noninfected patients.

Thirty-one patients suffering from arthritis associated with gonorrhoeal urethritis were treated. Most of these cases were acute or subacute, but some were of 5 months' duration, and many were over 10 weeks' duration when the treatment was begun.

As might be expected, the most striking results were obtained in the acute and subacute cases; however, the most refractory instances were also in the acute class. Those suffering for long periods appeared to respond more slowly to the treatment, but fortunately seemed to suffer from no recurrence or new joint involvements during the course of the treatment. All but 3 of the arthritic patients were apparently completely cured or manifested a decided improvement. The length of treatment varied from 2 days to 1 month.

Unusual effects were seen in 3 patients with acute arthritis, so severe that sedatives were necessary to give them rest for the first 2 days in the hospital. After a single reacting dose in each instance they felt so well that they insisted on getting out of bed, and in 3 days they walked from the hospital. Two of the patients had effusions in the knee joints, which completely disappeared before their discharge from the hospital. Equally striking was the instance of a man who had been confined to his bed for 4 weeks with arthritis of almost every joint of both lower extremities. These lesions had come on during the third week of gonorrhoea. After the third injection, he was

up and walking about, and after the 6th injection he was apparently completely cured.

The 3 refractory cases mentioned were all acute, and seemed not to respond at all or very slowly to this form of treatment. One would show considerable improvement for a day or two, but invariably would lapse back to the original condition; a second recovered completely excepting one knee joint, which contained a marked effusion and seemed not to be affected by repeated injections, while the third did not respond from the first to repeated injections of albumose solution.

Bruck noticed similar refractory cases which he explained by the absence of the homologous gonococcus strain from his polyvalent vaccine. It is evident that this explanation will not suffice, but whether it is due to a special resisting power of the particular infecting gonococcus or to some peculiarity of the infected host, it is impossible to say. Such patients react with fever and leukocytosis as do all others.

**Epididymitis.**— Twelve patients with acute epididymitis were treated, and invariably the pain would subside after the first injection. Usually not more than two injections were necessary, and indeed in most instances one proved sufficient to effect a cure. The swelling began to subside within 24 hours after the first injection. In no instance did the patient remain in the hospital over a week, excepting in one case in which an overdose was given.

That these injections are not prophylactic against the development of new complications is evidenced by the fact that occasionally one sees a patient under treatment develop an acute epididymitis or an involvement of a new joint. Again, a patient may leave apparently cured of arthritis to return in a few weeks suffering from epididymitis.

On account of the fact that the reaction following these injections is followed by a chill and general reaction of more or less severity, a very complete physical examination is necessary beforehand. Such a reaction necessarily calls for increased cardiac activity, so one should proceed with caution when a patient with coexisting organic heart disease presents himself. The smallest reacting dose of meningococci was given to one man who was suffering from mitral regurgitation of long standing but perfectly compensated, together with acute epididymitis. He passed through the chill with no distress, but in three hours after the injection he became cyanotic, his pulse became irregular and feeble, and he had marked precordial pain. This condition lasted 10-15 minutes, and he had no further inconvenience. No other cardiac irregularities were noted in the entire series. Arnold and Holzel cite Lewinski's case of acute cardiac insufficiency developing after the intravenous injection of gonococci. Heart disease was not known to be present. On the other hand, Luithlen reports a case of gonorrhoeal endocarditis successfully treated in this manner. There are many instances reported, however, of cardiac symptoms developing in the presence of organic heart disease following these injections,

so one should exercise care and judgment in the selection of cases.

**Renal Involvement.**—From the proper dosage in this series, there were noted no other symptoms attributable to the injections. Special attention was given the kidney function, particularly in three patients who had received large doses of colon bacilli. In no instance did albumin appear in the urine, nor did any indication of kidney involvement arise. One patient having a chronic diffuse nephritis with considerable albumin in the urine had two injections with no appreciable change in the kidney function.

This seems to be significant, as Breed and others had found that there is quite a marked increase in nitrogen output after such a reaction, this increase being maximum on the sixth day. She advises a low protein diet for a few days before such injections to prevent a possible kidney change.

Foekler reported epileptiform seizures after similar intravenous injections, and Fischer in one instance noted cerebral symptoms, which passed off in 24 hours.

Delirium was noted in three patients of this series, all of which had received large doses of colon bacilli.

Culver was particularly impressed with the possibility that the febrile reaction itself, the mere increase in the body temperature might be involved in the therapeutic effectiveness of the nonspecific therapy. A number of observers who at former times considered this factor in resistance to infection and recovery from disease, among them Walther, Hildebrand, Englehardt, Rolly and Meltzer, have reached the conclusion that high temperature artificially produced has a favorable influence on any established infection; on the other hand, cold seems to retard the formation of immune bodies. The optimum temperature for the growth of the gonococcus *in vitro* is 97°-98° F. Any appreciable increase in temperature has a very deleterious effect on the life and growth of the organism. A sudden rise to 102° F., or over, means certain death of the culture.

When acute epididymitis develops, does the fever produced thereby have anything to do with the spontaneous cure of gonorrhoea? Many patients with infections terminating thus have had considerable fever during the onset of the complication. On the other hand, patients are seen with infections terminating in a similar manner having had a normal temperature throughout; this, however, does not seem to be a common occurrence.

Experimental urethritis in man has been produced, but Finger, Gohn, and Schlagenhauser regularly failed when the experimental patient had a temperature of 102.2°-104° F. due to some preëxisting disease.

Culver calls attention to a patient who entered the hospital with acute urethritis of 3 days' duration. A positive gonococcus culture was obtained on entrance. The second day in the hospital he had a

chill, followed by a temperature of 105° F. Malarial parasites were found in the blood, but the chills and fever were allowed to continue for 4 days, at the end of which time all evidence of local infection had disappeared. He remained in the hospital for 2 weeks, without recurrence of the infection, having had no local treatment whatever. The influence of fever on these infections in the medical wards is of course well known; one rarely, if ever, sees a gonorrheal infection coexisting with some fever-producing disease like pneumonia, typhoid, or malaria while gonorrheal infections are relatively common among the chronic nonfebrile conditions.

The therapeutic results in the group which forms the basis of this report very noticeably correspond to the temperature increase and to hyperleukocytosis. Considering the fact that the gonococcus is heat sensitive both *in vitro* and *in vivo*; that fever patients cannot be experimentally infected with the gonococcus; that a fever-producing disease spontaneously cures previously existing gonorrheal infections, there can be but little question that fever artificially produced plays some part in the recovery from these infections.

How much influence, if any, the leukocyte increase in the peripheral circulation has, cannot easily be determined, for when artificially produced in the manner employed here, the fever and hyperleukocytosis are invariably present together.

It is apparent that the usual treatment of gonorrheal arthritis is not satisfactory in all instances, when almost daily one can see an ankylosed joint and atrophied muscles following this condition. Should this treatment by intravenous protein injections prove to give permanent results in this condition, as present data seem to indicate, are we justified in using such a measure? In view of the chronicity of the disease and the destructive complications that commonly arise it would appear to be a rational procedure when properly used and controlled. However, until some substance is obtained whose dosage can be more definitely standardized, it would seem that this form of treatment should not be generally used by those not thoroughly familiar with the reaction and the manner of regulating the size and interval of dosage of such, as used in the work here reported.

In a recent review of his work Culver states that in his experience at one of the military camps during the war where intravenous injections of gonococcus protein was made in every case of epididymitis, the results were most satisfactory, the average stay in the hospital being from 5 to 6 days. Even the primary localization of the organism in the urethra or extensions of the infection into the prostate and seminal vesicle responded more readily to local treatment after nonspecific injections of this kind than cases not injected.

Since the publication of these papers by Culver a considerable literature on the subject has been accumulating, all of which reveals practically the same general clinical experience—namely, that non-

specific therapy is of decided usefulness in the treatment of gonorrhoeal complications, either local or remote, but that in the treatment of the primary infection of the mucous membrane itself our older methods are of greater value and dependability, although certain observers are of the opinion that as an adjunct method of treatment it has its decided value even here.

Keyes makes the following statement: "It is not generally appreciated that the reason for the extreme susceptibility to recurrence of joint lesions with each gonorrhoea, in a patient who has once had arthritis, is a susceptibility in the joint, not in the urethra. At its onset the use of vaccines or serum may be worth while. Two or three doses of antigonococcus serum at the moment when a joint is beginning to become inflamed may abort the infection, as may also a heavy dose of gonococcus vaccine; this usually by the systemic reaction produced.

"But once the joint infection is established, vaccines are not to be relied on. I have tried all the specific and nonspecific forms that have been commended to me, including horse serum and typhoid vaccines administered intravenously. If these are employed in sufficient dose to give a systemic reaction, a temporary benefit may be obtained, and occasionally a permanent benefit. But the rule is that these treatments do not appreciably influence the course of the disease."

Luithlen has had considerable experience in the treatment of gonorrhoeal complications, using an intravenous injection of gonococci (100 million to the c.c.) as a rule to elicit the reaction; he specifically recommends, though, that local treatment should in no instance be neglected. In the treatment of old torpid venereal ulcers, soft chancres and ulcers persisting after buboes he injects about 50 million organisms intravenously two or three times at intervals of several days, or if intramuscular injection is preferred injects from 300 to 500 million, in some cases as much as 800 million organisms.

Bloch, who recognized that the vaccine therapy as used in intravenous injections was really related to our older method of counter-irritation or "Ableitungs-Therapie," has also used gonococcus vaccine and typhoid vaccine in gonorrhoeal complications, the latter especially in gonorrhoeal rheumatism. He obtained the best clinical result with the severest clinical reaction, in some instances the temperature reaching 106° F.

Gow has also tried out a diphtheroid organism intravenously (using first a dosage of 40 million, later 200 million) in a case of gonorrhoeal arthritis. There was relatively little reaction from this organism, a chilly sensation was noted about 14 hours after the injection, a rise of 2° F. in the temperature 2 hours later, and some headache. A leukopenia followed the injection. The result was not very satisfactory.

Konteschweller in his review of "pyretotherapy" states that he has obtained very satisfactory results in the treatment of gonorrheal rheumatism. He used milk, kephyr and peptone to elicit the reactions. Pakauscher uses "Fulmargin," an electrically prepared colloidal metal; this gives little general reaction but seems to be useful nevertheless in the treatment of gonorrheal complications. Ullmann mentions the successful use of milk in gonorrheal arthritis; Fraser and Duncan have recently reported on the treatment of a small series of such arthritic cases treated with intravenous vaccine injections. The vaccines they used had been stored for several months after their preparation, and they were, therefore, probably more or less detoxicated. Whether a detoxicated vaccine has any specific properties or not requires proof. They suspect that a vaccine minus its endotoxin consists simply of non-specific proteoses in a colloidal form. The injection of these, possibly nonspecific constituents, would seem to have caused the production of specific antibodies. Clinically they seemed to get the same result from injections of T.A.B. vaccine as from a gonococcus or mixed vaccine. The chief reason for using a gonococcus vaccine was that a supply was available, and its use afforded a great facility for graduating dosage. Freshly prepared typhoid vaccine often causes so severe a reaction that they would not risk giving it intravenously. Injections of endotoxins always produce toxic symptoms with but little or no increase of antibodies. Marked improvement followed in all of the fifteen cases treated. No benefit seemed to result from an injection that was not followed by pyrexia. At the time treatment was commenced, the patients were extremely debilitated with a rather fast and weak pulse, which was easily accelerated. The injections were all intravenous. The size of the doses used compares favorably with the doses recommended by Thomson for his detoxicated vaccine. The largest dose of gonococci was 2,000 millions.

The *myositis* of gonorrheal origin has been favorably influenced by intravenous injections of "arthigon" by Sachs while Reichmann has described a favorable influence of collargol injections in the treatment of gonococcus *endocarditis*.

**Local Injections.**—The use of milk, recommended by Müller and Weiss, has been quite extensive not only for intragluteal injection and systemic reactions (Gellis and Winter) but for local injection in or about the complication. Weiss has treated a number of cases of epididymitis in this manner, injecting from 5 to 10 c.c. of milk subcutaneously in the scrotal skin, and obtained excellent results.

This treatment by local injections about the site of the lesion was commenced by R. Müller who observed that if serum was so injected it improved localized disease processes. Sandek then treated some 100 cases of gonorrheal complications with this method and obtained excellent results. The analgesia following the injections was astonishing.

Sandek found that if he injected salt solution or potassium iodid in from 1 to 5% solution he obtained results that were similar in many respects. There was of course no general systemic reaction when the treatment was carried out in this manner.

Eisel has continued observations on this method of local injections of physiological salt solution and has reported on 30 cases in which from 10 to 15 c.c. of physiological salt solution were injected between the scrotum and the tunica vaginalis. He states that the pain was lessened very promptly and resorption of the inflammatory exudate facilitated in all of the cases of epididymitis so treated.

Other observers have treated gonorrhoea and gonorrhoeal complications with tuberculin (E. F. Müller) and with turpentine injections. Pürckhauer, who has tried the latter in acute urethritis, considers such injections of value as adjuvants but not useful in bringing about complete recovery from the acute infection, his experience coinciding therefore with that reported with the use of the other related agents. Karo has also used turpentine injections in gonorrhoeal complications, adding a small amount of eucupin to the dose to lessen the local pain that follows when only turpentine is injected. The largest series treated in this manner is that of Krebs who has treated several hundred cases of acute and chronic gonorrhoea, with particularly good results in the severer infections. According to his report the course of the acute disease was shortened and complications lessened. Injections were given every three to five days; after the second injection local treatment was commenced with choleval or with potassium permanganate. While he considers that every case should have local treatment, the general treatment with the turpentine injections had a marked effect in lessening the pain and the secretion after a very short time.

Reenstierna has made use of a combined specific and nonspecific method of treating the closed gonorrhoeal complications. He injects not only a specific antigonococcus serum but with it a typhoid vaccine to give the general reaction. With this combined method he claims to have obtained very satisfactory results.

Franzmeyer has claimed good results in the treatment of acute gonorrhoea by using intravenous injections of collargol combined with local treatment. Sommerfeld, who treated 42 men and 10 women ill with acute gonorrhoea with collargol intravenously, did not find the results as satisfactory as local therapy. Cohn has reported the treatment of 86 men of whom only 13 proved refractory to the nonspecific therapy. Weber, too, has reported that as an adjuvant, the intravenous injection of colloidal metals is of benefit in the treatment of acute gonorrhoea. Nuclein has also been used (Boas) while Brown has reported on results with normal horse serum as well as diphtheria antitoxin. He observed that the dose of normal serum which had to be used to secure results was much larger than the diphtheria antitoxin.

On the other hand, Riecke has reported that he has never observed a single recovery of an acute gonorrhoea following the fever therapy unless local treatment was instituted. From our present knowledge of infections of the mucous membranes it is probable that in acute infections nonspecific therapy has a limited field as an adjuvant to local therapy, while in the gonorrhoeal complications it finds a much wider and more useful application.

**Buboes.**—Stark and Odstreil began the use of milk injections in the treatment of buboes, which, like the other gonorrhoeal complications, seem to respond very well to this form of therapy. Müller and Weiss had already noted that certain gonorrhoeal complications yielded quite readily to the milk injections and Müller himself has published some 25 cases of buboes treated by means of milk injections. With one exception all of these (17 early cases, 7 older ones) were cured without surgical incision. Müller gave injections of milk every 3-4 days using from 5-6 c.c. of milk for the purpose. Usually the local reaction reached its maximum in about 8-9 hours when the greatest pain was noted, after which the part affected became analgesic. In the treatment of the old cases an average of 5 injections of milk were made; in the earlier cases 3 or 4 injections sufficed for a complete cure. Trossarello has also reported on the successful use of milk injections in the treatment of buboes. In 15 cases the injections practically aborted the lesions.

Schneller treated but two cases with milk injections, but both made complete recoveries without surgical intervention.

Guzsmann has reported that milk injections are followed by excellent results in the treatment of soft chancres, while Antoni using aolan (casein) obtained equally good results in soft chancres and buboes.

Reichenstein used milk in both buboes and epididymitis. The buboes usually softened rapidly and were then incised; the epididymitis also showed retrogression shortly after the treatment was commenced. No more than three injections were ever necessary.

Almkvist treated 8 cases of buboes with turpentine with tuberculin and with nuclein injections. The cases all made a rapid and complete recovery.

Kraus, on the other hand, treated 20 cases of gonorrhoea (acute) with milk injections (5 to 8 c.c.) without much apparent benefit. In 7 cases there was no general reaction to the injections; the focal reaction likewise was not marked in any of the cases. Grabisch, using turpentine injections, obtained favorable results in gonorrhoeal complications such as buboes, cystitis and even pyelitis.

Karo, who has recently employed "terpichin," a turpentine preparation combined with quinin, has reported on the use of this agent in a very large series of cases. In acute gonorrhoea he has used it in combination with the usual local treatment but considers that the

injections shorten the course of the disease as well as prevent complications. The ordinary complications are relieved in a very short time and even the arthritis is very favorably influenced.

**Provocative Reaction.**—In a recent paper Müller has discussed a subject that is of considerable and increasing importance in the genito-urinary field, namely the provocative reaction in male urethral gonorrhoea. While I have referred to it more fully in the chapter on focal reactions, a note of it should be made at this place.

We are familiar with the effect of alcoholic excess on the course of an acute gonorrhoea. Many of our modern therapeutic methods are frequently followed by a similar provocation of a latent gonorrhoea (such as the use of bougies, Kollmann dilatation, silver salts in higher concentration, hydrogen peroxid, etc.), and their use is followed by an increase in the discharge and the finding of organisms in the smear. On examination it is observed that the copious leucocytic discharge consists of fresh leukocytes, not old forms which may have been present in the focus for a longer period of time. They are the result of a myelotic stimulation that is induced by the reaction when the gonococci are stirred up at the focus, and are therefore to be regarded in the nature of a defensive reaction. Every procedure that first lowers the resistance—either locally as with the variout traumas mentioned, or generally, as after alcohol, after an intercurrent disease, after a nonspecific vaccination—is followed by this myelotic stimulation and an increase in the discharge. If provoked by a local method new paths may be opened for the spread of the infection, and it therefore entails an element of danger. Müller noticed that the intracutaneous (first used by Hecht) injection of aolan (casein) was followed by a marked effect on the infections of the mucous membranes and in applying this to gonorrhoea found that in from 6 to 8 hours after the injection there was noted a distinct itching of the urethra, followed by an increased flow of pus and usually the possibility of demonstrating the presence of the organism within 24 hours after the injection. Nevermann has applied this reaction with success in women.

**Adnexal Inflammation.**—It will be recalled that Kraus in his early work with heterovaccines found that he could definitely terminate the fever of puerperal sepsis in a number of cases when colon vaccine was injected intravenously. Since that time a number of observers have been interested in treating not only such cases, but adnexal inflammation in women due to other causes—venereal infection, tuberculosis, etc. For this purpose several methods have been used—milk injections, salt injections, colloidal metals, turpentine injections, etc. In general it may be stated that in this form of inflammation the single shock dose—whether milk or vaccine or colloidal metal—is less satisfactory than any form which is carried out over a longer period of time and is milder in character. Considering the

extent of the inflammatory changes and their peculiar character this result might be anticipated. In general it may be stated that the findings that hold true for venereal infection in the male hold true in the female, that is, that the acute infection, either cervical, urethral or uterine, is not influenced very much by this form of therapy, that the complications, on the other hand, are remarkably amenable to treatment and at times give exceptionally good results.

Menzi treated 117 cases with collargol injections, using from 2 to 10 c.c. of a 2% solution every two days. He states that of 34 cases of urethral gonorrhoea, acute and subacute, 23 became negative bacteriologically. Of 7 cases of chronic urethritis, all became negative. Of 24 cervical infection 23 became negative. Two cases of uterine infection were unchanged. Lux, who obtained good results in gonorrhoeal complications with injections of collargol, obtained negative results in acute infections, and Sommerfeld, too, did not see that in acute cases the treatment was as efficacious as local treatment. Kleemann treated 51 patients of this type with injections of 2% collargol; of these 11 were cured, 20 improved, while 20 were not altered clinically. Kleemann is of the impression that the injections shorten the course of the disease and when combined with local treatment are of manifest assistance. Infections of the uterus were also found by him to be refractory. Konteschweller recommends "pyretotherapy," produced by any of the common nonspecific agents, as of value in tubal inflammation.

Gerstein, working at the clinic at Halle, had used milk injections, but the general effects were at times rather unpleasant so that Kauert first used aolan (casein preparation). With this he treated 16 cases of pyosalpinx. Only one case reacted with a temperature rise and there was practically no leukocytic reaction. In these cases Kauert saw very little clinical change. Not obtaining any results with the aolan Kauert turned to milk injections, but here, too, his results were not successful. This corresponds to the results reported by Chiaudano.

Trossarello gave parenteral injections of milk in the treatment of forty-five cases of gonococcus infection and in fifteen cases of venereal bubo. In the apyretic there is an interval of two or three hours before the chill follows the injection, and this allows ambulatory treatment as the patients are able to reach home before it. No benefit was apparent in the cases of urethritis, prostatitis, epididymitis and arthritis, but in ovarian and tubal disease marked benefit was realized. All were improved, some after a single injection. His results in these twenty cases of adnexitis surpassed, he says, those obtained with specific vaccines or antiserums; the pain subsided promptly even before any objective improvement was apparent. He injected into the buttocks 5 or 10 c.c. of ordinary milk, at intervals of three or four days, to a total of five injections. The febrile reaction seems

to be the main factor; the best results were noted in the patients that presented the strongest reactions.

Arweiler, working with Lindig on casein injections (intravenous), reports satisfactory results in adnexal inflammations, the tumor masses showing definite regression and the patients a general improvement in condition.

Schönfeld tried the method recommended by v. Szily and Stransky (salt abscess) in 36 cases of acute and subacute gonorrhoeal infections in women. They obtained very poor results; only those made a recovery in whom abscess formation occurred. The method is painful and certainly not to be recommended.

More recently a number of clinicians have tried the method of turpentine injection with evidently more success. Fuchs, as well as Schubert, while in military service, had tried intramuscular turpentine injections in suppurating wounds without any effect (where we already have a large suppurating surface from which necrotic products are being absorbed, this result is to be anticipated), but found that when used in adnexal inflammation he obtained quite remarkable results. Zoeppritz and Kleeman had previously reported a fairly large series of cases and Fuchs reports 30 gynecological cases treated by the injection of 0.5 c.c. (of 4 parts of turpentine, 0.2 part of eucupin and 16 parts of olive oil) every 4 days intramuscularly. The site of the injection was the axillary line just below the crests of the ilium, injection being made very deep.

Kleemann's cases numbered over 60 and included all varieties of adnexal inflammation. In this series 36 were completely cured, 21 improved and 3 were not improved. He observed that the fever as a rule diminishes after a short time and the size of the adnexal tumor decreased until in many instances it was no longer possible to palpate the mass. He used turpentine with a small amount of novocain to prevent local pain after the injection.

The cases selected were bilateral adnexal inflammations, with the tumor masses varying in size from 2 to 10 cm. in diameter, with occasional temperature, menstrual disturbance—pain, bleeding, etc. In five of the cases a chronic gonorrhoea was manifest. The results of the treatment were very satisfactory, convalescence being established much sooner than with the ordinary local or expectant treatment. Not only was the local tumor mass reduced in size—Fuchs states that the large masses reduced in two weeks' time to the size of a walnut—but the patients felt better in general and the appetite was stimulated. Occasionally a temperature reaction of from 1° to 2° C. was observed following the injection; these cases gave the most striking clinical improvement. In no case did he have any untoward effect or find any injury from the treatment; in over 200 injections there was no abscess formation.

According to Fuchs the treatment is of very definite gynecological

value, even in the treatment of early adnexal inflammation accompanied by acute symptoms and much pain and profuse hemorrhage. The pain diminishes after the second injection, menstruation becomes normal after the next period and the adnexal swelling is reduced. The fact that these results can be achieved with an ambulatory treatment is of further advantage.

Sonnenfeld has also reported on 115 cases of gonorrhoea as well as nongonorrhoeal adnexal inflammatory lesions treated with turpentine injections. He considers the method of tremendous advantage in the conservative treatment of inflammatory conditions of this type.

Hellendall states that when on the basis of thirty cases Zöppritz demonstrated this method recently before the Verein der Aerzte at Düsseldorf, no adherents championed it during the discussion that followed, while Pankow presented two series of cases, one treated with and one without turpentine, and emphasized that the results indicated that there was no difference between the old conservative treatment and the turpentine treatment so far as the final effect was concerned. In Hellendall's own case, that of a young woman of 19, the ineffectiveness of turpentine injections was shown by a later operation, although it was a case in which good effects should have been apparent, if ever. Kronenberg is also of the opinion that the turpentine injections are without influence on the course of adnexal inflammation.

Hinze reports 205 cases, 35 of which came to operation; 65 were treated by the usual conservative methods and 105 with turpentine. He injected 0.5 c.c. of a mixture of 0.1 gm. of turpentine oil and 0.4 gm. of olive oil, in the posterior axillary line from two to three fingerbreadths below the crest of the ilium. The long cannula prevents the fluid being ejected into muscle or subcutaneous tissue, which increases the pain unnecessarily. In addition, in most cases, moist heat and hot air or hot-water treatment were employed. The discomfort following the injections was not severe and usually subsided in from four to five hours, but in several cases the pain lasted from three to four days, sometimes radiating into the leg on the same side. In 8 of the cases of pyosalpinx either a cure or marked improvement was effected. The results were very favorable in the 52 mild cases. As a rule these cases could be dismissed as cured in from two to three weeks. In the chronic cases, the pains usually disappeared after a few injections, and when the patients were dismissed in three or four weeks the tumors had decreased considerably in size. Hinz's judgment, therefore, is that turpentine injections constitute progress in conservative treatment of affections of the adnexa. However, that recurrences are not uncommon goes without saying.

Other observers have used autoserotherapy (Ishikawa) and Hasenbein has used injections of sugar solutions.

## CHAPTER XI

### INFECTIOUS DISEASES

#### ANTHRAX

The treatment of anthrax by means of injections of normal beef serum is a procedure inaugurated by Kraus and his associates, and has been discussed by them in a series of articles. They use beef serum twice heated to 56° C. for 30 minutes and inject from 30 to 50 c.c. or more intravenously or intramuscularly. According to Kraus' recent address, over 380 cases have been treated by him with this method with a mortality of less than 6.2%, as contrasted with the mortality of about 10% with expectant treatment. The injections are made repeatedly, usually in 12 hour intervals, although as a rule not more than three injections are necessary. Serum sickness has seldom been observed.

Solari reports the results in 6 cases, all of which recovered. Langon treated 13 with similarly satisfactory results. Lignières, however, was not able to confirm these findings.

Recently several experimental studies have been reported dealing with the problem, including those of Turro, of v. Hutyra and Maninger, Gerlach, Kraus and Beltrami and of Kolmer, Wanner and Koehler. The latter observers were able to determine some degree of bactericidal property in the normal beef serum, but hardly sufficient to account for the marked clinical effect induced by the serum injections. Heretofore it had been assumed by a number of clinicians that the effect of the beef serum might be due to the content of natural anti-anthrax amboceptors in the serum of the animals used for injection, because of the possibility of a degree of immunity present in the serum of cattle where anthrax is prevalent.

v. Hutyra and Maninger's tabulated results show that no protection was afforded rabbits inoculated with anthrax by treatment with normal beef, horse or sheep serum.

#### DIPHTHERIA AND DIPHTHERIA CARRIERS

One of the most remarkable reports concerning the application of nonspecific methods in therapy has been that of Bingel, which has created considerable discussion because it throws doubt on the specific value of our most widely used and most representative of specific sera, namely diphtheria antitoxin.

Bingel treated 471 cases of diphtheria with diphtheria antitoxin

and 466 alternating cases with empty horse serum—that is, normal horse serum which contained no antitoxin. The results as far as could be judged in the two series showed no difference in the mortality, in the duration of the illness, or in the number of complications. As a matter of fact Bertin is said to have used injections of normal serum as early as 1895 in diphtheria, and Rolly as well as v. Strümpell also employed “empty” serum. In 1912 Lorey again called attention to the subject.

Attention is called to Bingel's paper not because it describes a desirable mode of procedure that is to be commended, but because of its theoretic and practical importance. There can be no doubt that specific antitoxin will exhibit incomparable superiority over normal horse serum both in practical therapeutic application and in animal experimentation. But in practice the observation of Bingel has been confirmed, even if not in a large series, by Dorn and by Meyer. Klotz has recently reviewed the entire subject.

There has been an often expressed observation among a number of clinicians during more recent years that the modern highly concentrated diphtheria antitoxin does not always give the same satisfactory results that our older, less concentrated preparations did. Of the older preparations larger doses of serum had to be injected. The work of Bingel makes clear the basis for this conviction. That is, we are dealing in diphtheria antitoxin with two factors that are of therapeutic value, the specific antitoxin content and the nonspecific stimulating property of the serum proteins. The more highly concentrated the preparation, the less of the nonspecific element will be retained. This is probably the reason that the more modern serums have at times seemed followed by less therapeutic effect than the former preparations. As a matter of fact when some of the older literature is reviewed one finds observations concerning the temporary rise in temperature following diphtheria antitoxin injections, as well as the temporary leukopenia and the later leukocytosis that we now recognize as part of the phenomena that follow after the various nonspecific injections (Ewing).

A number of investigators have repeated Bingel's method, using the method of toxin neutralization in guinea pigs. Calhoun, for instance, as well as Kraus and Sordelli, found a slight protection with normal horse serum; other observers have found little or no protection. The lack of confirmation in animal work does not, however, rule out a therapeutic effect in human diphtheria. Lüdke has for instance treated 15 cases of diphtheria in adults with albumoses. (2-3 injections of from 3-5 c.c. of a 10% solution.) The therapeutic effects were quite comparable to those obtained with specific serum therapy. In 7 cases the first injection was followed by a complete disappearance of the diphtheritic membrane and the return of the temperature curve to normal within 24 hours. In three cases in which a stenosis already

existed the injections were followed by an increase in the swelling and the stenotic symptoms, the usual effect of nonspecific injections on local inflammatory processes. In 5 cases there was no apparent effect on the disease.

Paschen has used milk injections to free diphtheria carriers of their throat infection. Of 54 cases 37 were free in from 4 to 6 days, 7 in 14 days, while in 10 cases there was no effect of the injection on the throat culture. In emphasizing the fact that the high fever is one of the factors that aids in overcoming the condition, Paschen points out the fact that of these 10 refractory cases 5 did not react with any fever to the milk injections.

Müller has also reported that nonspecific injections—milk and casein—are effective in ridding the mucous membranes of the throat and nasal passages of diphtheria infection in the case of chronic carriers.

### BACILLARY DYSENTERY

The war with its attendant epidemics of dysentery both in the military forces and in the civilian populations afforded European clinicians considerable opportunity to study not only the prophylaxis but the therapeutics of the disease as well, and we now have reports available from a number of sources. Among them Nolf has published several papers which are available in the American literature dealing with both specific and nonspecific intravenous therapy; Adler was perhaps the first to report on the use of milk injections; Holler, in his large series of infectious diseases treated with deuterioalbumose injections, has included 50 dysentery cases and Döllken has reported a number treated with milk injections.

Inasmuch as Nolf's experience was quite extensive, at first with specific serum therapy, then with vaccines subcutaneously administered and later with intravenous bacteriotherapy, it may be of interest to quote extensively from his recent paper.

"The treatment of ulcerative dysentery gave us only temporary results so long as we had recourse to the methods of the books. Specific serotherapy proved futile. Therefore, because of the inefficacy of these methods, we had, toward the end of the epidemic of 1917, employed vaccinotherapy in the chronic cases that remained. When possible to isolate a dysenteric germ from the intestine, we made and employed an autogenous vaccine; otherwise we used a vaccine of a Flexner bacillus type made from a gelose culture killed by heat. At this time the vaccine was administered subcutaneously, in progressively increasing doses, the initial dose being usually 10,000. To obtain the desired result it was necessary to raise the dose frequently to from 5 to 10 billion. These large amounts of sterilized culture are regularly well tolerated, though often during from twelve to twenty-four hours after the injections, one observes a little fever, headache and lassitude, with more frequent and less consistent stools, sometimes

slight colic, and at the site of injection a little infiltration with moderate pain. All these sequelæ soon pass away and, as a rule, disturb the patient but little.

#### "VACCINOTHERAPY IN OLD CHRONIC CASES

"In the winter of 1917-1918, we still were receiving cases of chronic dysentery of which the onset dated back several months or several years. We applied the same treatment, but with this difference, namely, that the initial dose was regularly a million germs, and that the dose was raised progressively up to from 5 to 10 billion. The results obtained continued to be favorable. In every case the general condition was improved, and the intestinal symptoms steadily decreased. In the majority, the cure was complete and definite. At times there seemed to be complete cure at the end of the treatment, but at a later period the symptoms returned. In some cases the stools, although regular and only one or two a day and without blood and mucus, yet remained soft, and there persisted a little intestinal instability and discomfort.

"We should probably have continued the subcutaneous method of administration of the vaccine, had we not, in other affections, particularly bacteriuria due to the colon bacillus or the staphylococcus, observed that the intravenous method of administration was more efficacious and more rapid in its effects. We therefore began the administration of the vaccine by the intravenous route in bacillary dysentery.

#### "THE INTRAVENOUS METHOD IN ACUTE DYSENTERY

"We applied the treatment not only to those with confirmed ulcerative dysentery, but also to all those in whom the course of the disease made one fear the development of the ulcerative form, that is to say, in every case in which, after one week, a dietetic and drug treatment had not brought about a cure, or at least promise of a speedy cure.

"The doses were given at four-day intervals, the initial dose being regularly 10,000 germs, then 30,000, then 50,000, then 1,000,000, etc. In general, the betterment of the patient did not long delay. The fever dropped by lysis, with some recrudescences more or less marked on the days of the vaccine therapy and the next day; and the intestinal symptoms improved coincidentally. In many cases of moderate intensity a complete cure was effected when the dose of 500,000 was reached. In the more refractory cases, it was necessary to push the vaccine up to about 10 million.

"In fifty-two cases treated in this way, we had only two deaths. All the other patients left the hospital cured, except two whom military necessity forced us to send away too soon. We have no doubt that in these two cases also the continuation of the treatment would have resulted in a cure in a relatively short time. By vaccinotherapy we were thus able to avoid the dangerous tendency toward chronicity which in 1917 was produced in a considerable number of our patients. This last result we considered particularly gratifying.

"The complete record of the epidemic of bacillary dysentery of 1918 shows a complete cure, at the latest in a few weeks' time, in 500 cases except only two patients who died, and two who had left before the cure was complete.

## "CONCLUSIONS

"I believe I am justified in concluding from these observations that vaccino-therapy and more especially vaccination intravenously is the most effective therapeutic method in bacillary dysentery in its chronic forms and in the acute forms that show little tendency toward cure. It appears also that the method is more efficacious when it is applied early. The intravenous route has the advantage that it permits results from doses one-thousandth the size of the subcutaneous doses. Not having had occasion to try this method in cases of Shiga bacillus desentery, it is impossible for me to speak of its utility in this form of dysentery.

"In acute dysentery, intravenous vaccino-therapy cures quickly in cases exhibiting protracted fever and lasting diarrhea with hemorrhagic and slimy stools, these being the cases that are refractory to other therapeutic methods, including serotherapy."

Of course, the bacteriotherapy is not a specific procedure; the same effect can be obtained when the reaction is produced by any of the other agents.

Milk injections, first used by Adler in dysentery and cholera, were also used by Döllken, who employed them because of the marked styptic effect following intramuscular injections; he did not, however, observe any actual change in the coagulation time of the blood of dysentery patients before and after the treatment. It is to be assumed that in the early stages of dysentery when hyperemia and engorgement of the mucosa are not yet pronounced and where we are dealing merely with small petechial hemorrhages and a hypersecretion, the injections will be followed with the best clinical result and this is actually found to be the case in clinical practice.

Döllken injected 5 c.c. of milk intramuscularly (occasionally less). Sometimes after 5 or 6 hours a definite focal reaction was to be observed in the form of increased evacuations containing more blood. The recovery was very prompt after this period. Usually the first day after the injection the blood was considerably less, even absent in some stools. This was observed to continue after the second injection. Usually after 5 days blood was no longer present. The spasm of the small bowel was almost always relieved after the first injection; the tenesmus in 4 or 5 hours after the first injection. An interesting fact was noted in regard to those cases that had had albuminuria. This was invariably gone after the injection.

Contrary to the experience of Nolf, Döllken did not observe much effect on the temperature curve after the milk injections, although in some cases a defervescence was noticed after the second injection. In cases treated with specific sera and vaccines this same lack of effect on the temperature of course holds true.

In more advanced cases the ulceration does not yield to treatment so readily. After about 5 days, however, improvement is noted in

the tenesmus and obstipation, but the hemorrhages are apt to persist longer. In cases that have diphtheritic membranes Döllken obtained good results after repeated injections.

Of theoretic interest was the fact that in cured cases Döllken was at times still able to cultivate the causative organism (Flexner) from the stool; the agglutination titer of the patient's serum, no matter what the clinical outcome, was not altered by the milk injections, but after specific vaccination was increased.

Deutero-albumose, tried in several cases by Döllken, was not as satisfactory. Holler, on the other hand, has treated 50 cases of bacillary dysentery (Kraus and Shiga) with daily injections of deutero-albumose and in this series had only two deaths.

Lüdke treated 14 cases of severe dysentery (12 Shiga and 2 Flexner Type) with deutero-albumose injections (3 to 6 injections of from 1-2 c.c. of a 10% solution). Apart from absolute rest in bed, heating pads, and proper diet, there was no other therapy used in these cases. In from 3 to 6 days 12 patients were markedly improved—the stools were normal and free from blood or mucus, tenesmus had disappeared and the general condition and appetite returned to normal very rapidly. In two cases, in which an earlier effort with serum therapy had been unavailing, the injections of deutero-albumoses was also without effect.

Furno treated 5 cases of hemorrhagic dysenteriform colitis, due possibly to mixed infection, with intravenous injections of proteoses (10 to 12 c.c. of 10% solution). He found that by prompt therapy of this kind the disease is arrested before it reaches the ulcerative stage.

Reiter found on the other hand that in a small series of cases only one case actually improved. Schelenz, using polyvalent serum and also injections of dysentery vaccine, found that while the course of the fever was not altered very much, the blood disappeared from the stool, the diarrhea decreased and the general condition of the patient improved.

While specific serum has been used by many clinicians, general opinion seems to confirm the conclusion of Nolf that it is not of great value unless given in huge doses either intramuscularly or intravenously and frequently repeated. Pfeiffer used 100 c.c. of polyvalent serum irrespective of the bacteriological finding and gave five to six injections; usually a slight systemic reaction would be observed after the injections. The size of the dose necessary and the fact that it must be given very early if it is to be useful at all leads to the conclusion that the effect can only be found in the nonspecific stimulation by the serum, rather than in any specific antibody content. Schittenhelm's results would lead to the same conclusion. v. Scilly and Vertes made use of this feature by injecting their patients with "solusin," a rather toxic agent described elsewhere, from the use of

which they claim to have obtained results equally as satisfactory as from the specific serum injections.

### ERYSIPELAS

The treatment of erysipelas by means of antistreptococcal serum, usually by subcutaneous injections, is by no means a recent procedure, nor one concerning the value of which an agreement has been reached by clinicians. Chantemesse used Marmorek serum in some 500 cases and gained the impression that the process of recovery was accelerated. After 24 hours the swelling, induration and pain began to diminish while within a few hours after the injection the general condition of the patient improved. Jochmann, who had a considerable experience, concluded that where the local inflammation was to be influenced, subcutaneous therapy was valueless, but that in the severely toxic cases with delirium, rapid pulse, etc., the effect of the serum was manifest in improving the general condition.

Since the introduction of the intravenous methods of administration of antistreptococcus serum, or with nonspecific methods, one can determine a more marked effect on the disease, both locally and in the general effect on the patient. Together with Jobling and Manier we commenced the treatment of erysipelas in 1915 with proteoses injected intravenously. The results in several cases have been presented by Jobling. Since that time the writer has had opportunity of observing a series of about 15 additional cases treated either with proteoses, milk, or typhoid vaccine and the results have in all cases been very satisfactory, indeed in some cases seemingly quite remarkable. The rapid subsidence of the intoxication, the general improvement of the sensorium and cardiovascular apparatus gave striking evidence of the decrease in the intoxication. The local process is also influenced, usually not, however, until there is evidence of the systemic effect in the euphoria and lessening of the toxicity of the patient.

French clinicians have used subcutaneous injections and oral administration of normal serum as well as diphtheria antitoxin in the treatment of erysipelas for a number of years (Launois, Darier, Apostolleau, Pollak and Mayweg) with some success, but in recent years the intravenous injection of such sera has evidently been followed by more apparent effects on the course of the disease. Koller, Uhlig, Basset, Campani, Frank and Bugolli report on cases so treated and Boyksen, who used normal horse serum, treated a rather large series. In severely toxic or extensive infection he administered 20 c.c. intravenously together with 10 c.c. subcutaneously; in the milder cases only 10 c.c. was given intravenously.

The colloidal metals have also been employed, at times with success. (Eberstadt, Cholewa, Capitan, etc.)

Holler calls attention to a fact which we have observed at vari-

ous times, namely, that intravenous injections of this kind may be followed by a very marked reaction on the part of the patient, so that even relatively small doses may incite a severe general reaction. Holler treated 32 cases of erysipelas with small daily injections of deutero-albumose, all of whom made a prompt and uncomplicated recovery. The reaction was, however, at times quite severe, in some cases the patients becoming delirious for a short period following the chill. Nolf has described the use of peptones, Kraus, Turnheim and Reichenstein obtained satisfactory results with milk injections while Blumenau treated 77 cases with nuclein injections. In this series the favorable effect was more apparent in the general condition of the patient than on the local process. Audain and Masmon-teil used sugar solutions; Engländer reports that following the intravenous injection of salt solution—100 to 150 c.c.—the temperature usually returned to normal very promptly; v. Szily and Schiller used typhoid vaccine successfully. A number of observers have obtained satisfactory results with either direct or artificial sunlight. (Bruce and Hodgson, Capelle, Klapp, etc.)

Schmidt has recently reported on a series of 52 cases treated with milk injections. Of these 44 involved the face, 4 the upper extremities, 3 the lower and in one case the abdominal skin was involved.

The results were as follows:

<i>Defervescence</i>	Face Cases	Upper	Lower	Abdomen
		Extremity		
1st Day after injection . . . .	27	2	1	1
2nd " " " " . . . .	8	2	2	..
3rd " " " " . . . .	4	..	..	..

Of the 4 cases that did not respond until the 3rd day, one had an angina, and two had a lymphadenitis colli (tuberculous).

The five remaining cases which persisted longer than 3 days were all complicated by other infections.

### INFLUENZA

The recent pandemic of influenza gave opportunity to study the effect of a great variety of nonspecific agents on the clinical course, particularly of the complicating bronchopneumonia, and a considerable literature has developed which can only be briefly reviewed at this time.

*Colloidal Metals.*—Teller reported satisfactory results with col-largol. Capitan, who treated 321 cases of uncomplicated influenza and 208 cases of bronchopneumonia of influenzal origin, used a colloidal arsenic preparation, which he had previously found useful in tuberculosis and syphilis. The preparation contained 3 mg. of arsenic and 2 mg. of silver per cubic centimeter, and of this from 6 to 9 c.c. were injected either intramuscularly or intravenously. He de-

terminated a favorable effect on the pulse rate and the general condition of the patient; the temperature usually declined in about 3 days after commencing the treatment. Van Andel and Heymans both used collargol in a small series of cases with favorable results. Hodel found both collargol and the fixation abscess useful in influenza. Holden used colloidal silver and Richard, Remond and Netter have also reported on the use of similar metallic preparations. Tail-lens treated some 300 cases of influenza and complications with a number of different agents. Salvarsan was not effective, euesol and galyl were also found useless; colloidal metals were only useful in very large doses.

Wachter used collargol in influenza and obtained good results if it was administered sufficiently early. In the pleurisy following pneumonias it was also useful. He recommends care if there is any nephritis present because he observed that several cases had a recurrence of casts and albumin in the urine after the collargol injections.

Witte also recommends such intravenous injections if they can be given early enough.

The *fixation abscess* and *turpentine injections* (collobiase) seem to have been used with considerable success. Tail-lens reports that injections of turpentine gave him better results than the other agents that he employed (see above). He used it in 38 cases. Netter, who treated 230 simple influenza cases and 309 cases with complications, found that his mortality was about 22%. Cases treated with injections of colloidal tin oxid were not influenced very much. He also employed normal serum and collargol without much effect. A fixation abscess was employed in some cases with perhaps better results. Pehu and Pillon claim to have found turpentine injections useful in the treatment of bronchopneumonia, especially in children. Netter, Vergely, Roumaillac and also Klingmüller used turpentine injections. Swiss clinicians have employed the fixation abscess with apparent success. Thus Hodel treated 156 cases of influenzal pneumonia. Of these 102 were treated with intravenous injections of electargol, the dosage being from 5 to 20 c.c. The mortality was 20%. In 15 cases treated with the fixation abscess the results were much better. Probst describes his experience in the epidemic of 1920 as well as in those of 1918 and 1919. His experience then and with recent cases has confirmed his previous announcements in regard to the benefit from a fixation abscess induced by subcutaneous injection of 1 c.c. of turpentine. He ascribes its efficacy to the hyperleukocytosis which it induces, as influenza is accompanied by pronounced leukopenia. He thinks this explains also why influenza is mild post-partum, because the hyperleukocytosis of parturition renders the infection mild, and there is nothing so effectual, he declares, to induce hyperleukocytosis as the fixation abscess. He warns not to incise the

abscess until the disease is subsiding (apyrexia), and then to make an ample incision and clear out the abscess thoroughly.

Niemeyer has used intravenous injections of *gelatin*, but only in a few cases.

*Milk* has been used by a number of clinicians. Von den Velden treated about 90 cases with serum, as well as milk, with results which he claims were very satisfactory. Of the milk 10 to 20 c.c. were injected intramuscularly two or three times during the course of the disease. Münzer and Pnitz also found that milk injections favorably influenced the disease. Patschkowski treated 40 cases of influenza pneumonia with milk injections (10 c.c.). Repeated injections were given if the effect was not sufficient after the first dose. In this series 8 patients died. He observed that the typical reaction of increased fever and a chill were often lacking when the injections were made in such pneumonic patients. Zalewski and Müller report very favorable results after the injection of aolan, a milk preparation that is not followed by a severe reaction.

*Serums.*—*Diphtheria Antitoxin* was repeatedly given a trial. Kautsky used injections of about 3,000 units and claims good results. Vaubel used injections of 1 c.c. in 20 cases with favorable results. Bettinger treated 18 cases with satisfactory results and Lustig treated 100 cases, all of which had pulmonary complications, with injections of 10 c.c. of antitoxin. The results were very satisfactory as contrasted with untreated cases in the same clinic. Crohn also reports 17 cases so treated. There were all uncomplicated influenza.

*Antistreptococcus Serum* was employed by Hughes and also by Grote. The latter treated some 40 cases with antistreptococcus serum, horse serum and convalescent serum and Maale has reported similar results. Friedemann has used a polyvalent serum in 20 cases and considered the effect favorable.

*Normal Serum and Convalescent Serum* have found extended employment, and seemingly with satisfactory clinical results. Reiss used normal serum, convalescent serum, normal horse serum and diphtheria antitoxin, injecting from 20 to 200 c.c. intravenously with excellent results. The temperature usually fell within 36 to 48 hours. Grigant and Montier made use of the plasma serum of Richet—a mixed rabbit plasma and human serum—which when injected early in the course of the disease was followed by satisfactory results. Other clinical observations have been reported by Pfeiffer and Prausnitz; Brodin, Lesné and Saint-Girons, Aguirre, Ehrenberg and Bachmann, Huff-Hewitt; Francis, Hall and Gaines; Holst; Ross and Hund, Luithlen and Winterberg, Bogardus, Pauly, Redden, Földes and Hajos, O'Malley and Hartman, Stoll, Liebmann and others.

*Vaccines.*—While a considerable number of observers have used specific vaccines as therapeutic agents, the reaction from the injection of influenza bacilli is not very marked and the nonspecific effect

therefore not pronounced. Gow, for instance, has injected 75 million or more organisms intravenously without producing a chill, but did observe a temperature rise of 2° F. after three hours. There is little leukocytosis to be observed from such injections. J. Black Milne has reported on the use of mixed vaccines and Snyder has treated 20 cases with intravenous injections of typhoid vaccine. There were no deaths in the series and Snyder considered the method of decided value. Cowie and Beaven have also used typhoid vaccine in the treatment of pneumonia but consider it of value only in the early stages of the disease. An extensive series of 200 cases has been reported by Roberts and Cary who employed a vaccine made up of 100 million organisms per cubic cm. of each of the following: influenza bacilli, pneumococci, staphylococci and streptococci. Of this vaccine they injected from 0.5 to 1 c.c. intravenously. In their series so treated there was no evidence of injury to the patients in any way. The mortality of the treated cases was 9.5%; in a series of 86 patients not treated with vaccine the mortality was 31.2%. In the treated series 36% recovered by crisis, in the untreated series 20% so recovered.

*Much's Vaccine.*—Much, Schmidt and Peemöller have reported on the use of a nonspecific vaccine made up as follows: Reactive proteins derived from a number of nonpathogenic bacteria; a lipoid mixture from bile and a fat mixture of animal origin. This so-called "immunvollvaccine" was elaborated on the basis of the "partial antigen" theory of Much's. They report satisfactory results with the vaccine in the treatment of influenza.

*Hypertonic Salt Solution.*—Borchardt and Ladwig have reported that they obtained good results following the intravenous injection of small amounts of salt solution (5-10%), as well as with convalescent serum. Their cases numbered 98; they remark particularly on the detoxication evident in the more severe cases.

*Albumoses.*—Ten severe cases of influenza were treated by Lüdke with *albumose* injections. In 5 of them an immediate effect of a single injection was apparent—the patients recovering by crisis. In 2 cases pneumonia developed together with empyema. Both made protracted recoveries. In 3 cases the temperature came down only after a number of injections.

#### LETHARGIC ENCEPHALITIS

Laubie and Marinesco report the rapid recovery of patients ill with lethargic encephalitis following intraspinal injections of tetanus antitoxin. Brill has also used spinal injections of serum. Grunwald has injected from 80 to 100 c.c. of convalescent serum intragluteally in cases of lethargic encephalitis. The effect on the temperature and pulse rate was prompt, lysis occurring in 3 days after the injection.

Neuralgias persisted for some time after the temperature had returned to normal. Voorthuis claims to have found the fixation abscess useful in encephalitis.

#### MEASLES

Both Holler and Müller have treated cases with albumose and with milk injections. Pehu and Pillon report that injections of turpentine were very satisfactory.

#### PAROTITIS AND ORCHITIS

Salvaneschi has reported that the injection of diphtheria antitoxin is of considerable value in the treatment of parotitis and in the orchitis frequently complicating parotitis. More recently Bonnamour and Bardin have reported 65 cases of mumps which had such treatment (20 c.c. of serum subcutaneously). Of these 57 entered the service without a complicating orchitis and none of them developed this complication; in 8 there was testicular pain on admission with a beginning orchitis which resolved promptly after the first or second injection. They consider the serum injections not only of value in the treatment of the orchitis, but as a prophylactic against the development of orchitis.

#### PNEUMONIA (LOBAR)

In the chapter on the Mechanism of the Protein Reaction the effect of injections on the course of lobar pneumonia has been discussed. As we might expect, severe reactions may be followed by a temporary defervescence, but they do not as a rule effect the pulmonary lesion when once it is established. One finds occasional references in the literature in which foreign protein therapy has been used with a measure of success (Monguzzi—milk and gonococcus vaccine, Talamon—diphtheria antitoxin, etc.), but the method cannot be considered of established value. On the other hand it is by no means excluded that when specific serum therapy is used (chicken serum, human serum, horse serum), or specific vaccine therapy (as for instance the Rosenow pneumococcus autolysate) part of the therapeutic effect may not be due to the protein injected. Injections such as those described by Huntoon (soluble antibodies) always bring about a marked reaction on the part of the patient and are effective only when given early in the course of the disease, observations suggestive of nonspecific effects.

#### PUERPERAL INFECTIONS

Lindig tried injections of casein in several cases of puerperal infection. One case had had a continuous fever for two months. Three

injections of 1 c.c. each were given intravenously. These were followed by chills which usually began one hour after the injection; some headache was also noted. After the first injection there was no temperature rise, nor was it marked after the second injection given the following day, but after the third injection was made 4 days later, there was a reaction of 2° C. The patient was completely cured after the third injection. Lindig treated several other cases with similar results.

The effect here noted in the temperature curve was reflected in the effect on the leukocytes. After the first injection there was usually only a slight leukocytosis, but with the second or third injection this was much more marked. A well-marked euphoria was observed in every case.

Kraus in his early work on heterovaccination found that he could bring the febrile course of puerperal infection to a prompt termination by injecting typhoid and colon vaccine intravenously.

Arweiler in a Dissertation has taken up the use of casein injections in considerable detail and Lindig has reported on the use of such injections as a method of prophylaxis in the puerperium. His report covers the results in 61 cases.

The colloidal metals have been used with some success (Siegel); Whitehouse reports success following the intravenous injection of Flavine; Werner has confirmed the earlier reports of Kraus in using typhoid vaccine. Gow uses Witte Peptone. The first dose which may be given intravenously to a septicemic adult is from 8 to 10 c.c. The quantity is increased by 2 c.c. every other day or so until 16, 18 or 20 c.c. are given at a time. The injection must be made slowly and for that reason Gow employs Nolf's technic using a record syringe and a very fine bore needle—with a No. 28 it is impossible to introduce the solution too quickly. In cases of puerperal septicemia the injection of peptone tends to cause an immediate and rapid fall in blood pressure, a rise in the pulse frequency, and if the patient has a leukocytosis, it rapidly induces a high degree of peripheral leukopenia—all these phenomena being of very short duration. Of these changes, the easiest to record as a guide is the pulse frequency, and while the injection is in progress the nurse keeps count of the radial pulse, calling out the number each quarter of a minute. Though he is convinced the peptone is a very valuable adjunct to sensitized vaccine, Gow makes no extravagant claim that it always brings a septicemia to an end, and he cautions any who may look for a dramatic and sustained fall of temperature after its use that most times they will be disappointed.

Bianchi gave parenteral injections of milk in thirty-six obstetric and twenty-one gynecologic cases. He reports that it seemed to promote and accelerate the cure in certain cases and ward off serious disturbances, but when severe puerperal septicemia was under way,

no benefit could be detected. Under any conditions the effect did not much surpass that from the ordinary measures, drugs, vaccines, fixation abscess, mercuric chlorid by the vein, etc. But the harmlessness of this milk form of protein therapy, its availability, and its excellent influence in reducing objective and subjective pain and in enhancing the defensive powers of the organism, impose its use on a large scale, he declares, especially during the early stage, when it is most potent.

### SCARLET FEVER

The treatment of scarlet fever by means of serum injections dates from the year 1897 when both v. Leyden and Weisbecker used the serum of convalescent patients in a series of patients ill from scarlet fever. Jochmann and Rumpel in 1903 tried subcutaneous injections, using a dose of about 20 c.c., without obtaining results that were particularly striking. Indeed the results from subcutaneous injection have in general been rather unsatisfactory, unless huge doses are used. It was not, therefore, until Reiss and Jungmann published their paper some years later that more attention was given the subject. Since that time Russian and Austrian clinicians have reported extensively on the use of antistreptococcus serum, with at times excellent results. Apart from convalescent serum, the antistreptococcus serum of Moser, prepared by immunizing horses with strains of streptococci freshly isolated from fatal cases of scarlet fever, has met with considerable success (Axenow).

In the earlier period the serum was given subcutaneously and the results were never striking. Reiss and Jungmann, however, used their serum intravenously and with this method of injection the results have been much more satisfactory. Convalescent serum being rather difficult to obtain in large quantity the injections have been limited as a rule to about 20-90 c.c., while with other serums the dosage has been much larger, several hundred c.c. being used. Jochmann, who followed this form of therapy for a number of years, considers that intravenous serum injections, if given early in toxic cases, lessen the toxicity, usually hasten defervescence and seem to lessen the number and severity of postscarlatinal complications.

Synnott has also reported on the use of convalescent serum and Weaver has discussed the question fully.

Glaser has recently reported a series of grave scarlet fever cases treated with pooled convalescent serum. In 15 cases it was given intramuscularly in doses of from 50-80 c.c. In 40% of these cases the temperature came down by prompt lysis. Complications did not seem to be influenced by the treatment. In 28 cases in which the serum was administered intravenously the effect on the temperature curve was apparent in every case. Occasionally the intravenous injection was followed by a chill, some headache and temporary weakness, but

he saw no unfavorable result from the injections. All recent observers insist that if effects from the serum are to be expected the same must be given within the first three days of the illness. (Rowe, Bennecke, Zingher, Koch, Moog, Reiss and Hertz, etc.)

Moog as well as several other clinicians used normal serum in doses of 80-100 c.c. In 25 cases 7 responded with a critical drop in the temperature; 13 dropped by lysis; 2 cases died, while in 3 there was no effect.

Rehde, who treated 89 cases, used normal serum in 14. In both series the results were equally satisfactory. Usually a mild, general reaction was observed following the intravenous injection, that is, the temperature was increased for a short time, a chill noted, as well as some headache. Griesbach in a series of 21 cases observed this reaction repeatedly in his series (8 out of 21 reacted with a chill) and 4 patients went into collapse. Krause, who treated 28 cases of scarlet fever with convalescent serum, also has observed collapse symptoms in a large percentage of the cases (25%). In his series there were, however, only 4 deaths and in 24 the temperature came down promptly after the injections.

This collapse observed by Griesbach and Krause is, however, quite unusual and Reiss, who has so far treated 221 cases, states that he has never had one case in which collapse and death followed the injection. Schultz and Ehrmann have also treated a large number of cases with intravenous serum injections. Ehrmann's cases numbered over 200 and his results were very favorable. He emphasized the importance of injecting early in the course of the disease if results are to be expected.

Schultz' cases numbered 184, of whom 102 were treated with normal serum, 67 with convalescent and 15 with both kinds of serum. He reports very apparent improvement in about 60% of the cases following the injections.

Prinzing has studied the effect of serum treatment on the complications with the following results: Lymphadenitis colli occurred in 15.5% of the injected cases, in 34% of the noninjected; otitis media in 9.3% of the injected, in 10.8% of the noninjected; nephritis in 8.2% of the treated and in 18.9% of the nontreated cases.

Holler has published a series of 32 cases of scarlet fever treated with injections of deutero-albumose (twice daily, 1 c.c. of a 10% solution). There were no deaths in the series and no complications. The course of the disease was in each instance shortened.

Lüdke treated 14 cases of severe scarlet fever with albumose injections. The fever very frequently ceased promptly after a single injection, the skin eruption likewise fading and the exfoliation began very promptly. There were no complications and no nephritis was observed. There was no doubt in Lüdke's opinion that the injections resulted in a material shortening of the course of the disease.

In general it may be stated that following the intravenous injection of convalescent human serum, normal human, as well as horse or other serum in cases of grave scarlet fever, the patient reacts with a slight increase in temperature and occasionally with a chill; in the majority of cases this is followed by a prompt lysis or crisis. The toxic manifestations of the infection are usually diminished, the patient feels better, complications are diminished in number, but preëxisting complications are not influenced appreciably.

There seems very little that is specific in the reaction, for it is immaterial whether immune streptococcus serum, convalescent serum, normal human or animal serum is used, or whether proteoses (albumoses) are employed. Even salvarsan, according to Jochmann, is followed by a typical reaction on the part of the patient, in effect similar to serum injection, so that he considers the employment of the one or the other merely a matter of individual preference.

### SEPTICEMIA

The treatment of septicemia by means of nonspecific injections has at times undoubtedly yielded brilliant clinical results; more often, unfortunately, there has been no apparent effect on the course of the disease. Perhaps the failures are due to the fact that nonspecific therapy has almost invariably been left as a final resort when the patient was quite exhausted and incapable of stimulation. It is to be remembered that the very fact that in the true septicemia we are dealing with bacterial proliferation in the blood stream and that thereby all parts of the organism are already being stimulated—or overstimulated as the case may be—makes any therapeutic application of this nature practically hopeless at the very start. Nevertheless one does at times witness quite remarkable and dramatic recoveries by crisis or by lysis after nonspecific injections. The older literature, in which the injection of colloidal metals was dealt with, is quite extensive and need not be reviewed at this time. The results were on the whole inconclusive. While recoveries were observed that seemed definitely contingent on the therapeutic injection; in other cases there was no apparent result. Reichmann (6 cases, 5 deaths).

In the more recent literature other procedures have been mentioned, some of which seem to have been followed by very favorable and consistent results. Brown has discussed the use of the metallic colloidal preparations. Hypertonic sugar has found advocates (Baradulin, Audain and Masmonteil), and immunized blood has also been used (Steel). Wright has suggested a method of using such immunized blood for transfusion. The mode of preparation is to treat the blood of a healthy individual with vaccine, then transfuse the infected individual with such immunized blood.

Kalberlah claims to have obtained very good results by injecting typhoid vaccine.

Gow has recently used peptone injections for intravenous injections in septicemias and has combined them with subcutaneous injections of streptococcus vaccine (sensitized). By this method he claims to have obtained excellent results; Nolf, too, has had success with peptone injections.

In two cases of streptococcus sepsis recovery occurred in 4 and 8 days respectively after intravenous injection of *deutero-albumose*. (Lüdke.) There was a very severe chill after the injections. In one case of tetragenous sepsis there was prompt recovery after a single injection.

Among the more recently introduced colloidal metal preparations "argochrom," a methylene-blue-silver combination, seems to have found considerable favor. Wendt treated 14 cases with this agent and considers it of value.

Weichardt in a recent paper which takes up the effect of protein therapy in the pneumococcus sepsis of mice, states that both Jaschke and Freund have obtained favorable results in septic cases with protein therapy.

#### SMALLPOX

Holler reports on the treatment of variola with daily intravenous injections of *deutero-albumose*. The results are described as satisfactory.

#### TETANUS

A rather remarkable experience is that reported by Lüdke in the treatment of 7 cases of tetanus. These were all cases in which severe spasm had developed after incubation periods of from 7 to 11 days. The treatment consisted of injections of *deutero-albumose* of from 3 to 5 c.c. of a 10% solution, given in 24- or 48-hour intervals. No specific serum and no magnesium sulphate was used. All cases recovered in from 7 to 22 days. Lüdke observed the characteristic effect of non-specific therapy on nerve irritability in that the spasms were first augmented after the injections, then diminished in intensity. Kaznelson also treated two cases with *albumose* injections. One case recovered, the other ended fatally.

#### TRENCH FEVER

Paul Jungmann treated a large series of cases of trench fever (Wolhynian Fever) with colloidal metals without result, despite the fact that a typical nonspecific reaction was elicited, with a severe chill, fever, etc. Often the patient was seemingly cured, with the temperature curve normal and the other symptoms in abeyance, but finally the clinical course of the disease again became manifest.

With typhoid vaccine and old tuberculin a similar reaction and effect was obtained, just as one finds that as a result of intercurrent infections, pneumonia, etc., the symptomatology of the trench fever may almost completely disappear. The nonspecific injections, according to Jungmann, had no direct effect on the course of the disease other than described.

Kirchberg, on the other hand, who used collargol intravenously, states that during the time that the patients were under observation there was no return of the fever after the injections, and the anemia was also markedly improved. Richter, too, found that collargol injections were followed by satisfactory results.

#### TUBERCULOSIS

In the discussion of the focal reaction and the relation of the skin reactions to nonspecific factors, evidence has been presented that tuberculins are active as non-specific agents and it should be kept in mind that their therapeutic effect can be accounted for largely on such a basis. In a general way the experience with tuberculins has been the following: Large doses in active cases cause a rapid progression of the disease, with cavity formation, increased tendency to hemorrhage, etc. Even small doses in active cases are not without some danger. In the inactive cases large doses may activate the focus; moderate doses may be followed by an improvement, or no apparent effect on the focus. In incipient cases large doses may occasionally be followed by complete and rapid recovery; more often though the effect is a harmful one.

Keeping in mind the fact that resistance to tuberculosis is largely cellular and that the effect of nonspecific stimulation is always at first associated with increased digestive phenomena, we might anticipate these effects. An active process will be made more active, an inactive one may be activated; on the other hand, a small incipient lesion may, by activation, digestion, etc., occasionally be rapidly healed.

In a general way this agrees with the experience that has been gained with protein therapy in the treatment of pulmonary tuberculosis.

Holler found that while early cases may react well and there may be an increase in the general resistance, advanced cases may give noticeable evidence of autolysis and extended cavity formation. Mueller found that if he treated cases with slight apical lesions and only moderate evidence of activity, the entire process might be cleared up after a few injections of milk. Naturally in such cases we bring about a decided focal reaction and the organism must be in physical condition to withstand and detoxicate all the necrotic material that is liberated by the digestion at the point of infection and to destroy bacilli that are freed in the process. If it cannot do this we will merely spread the infection.

Schmidt and Kraus report very remarkable results following milk injections in early tuberculosis; Klemperer has gone over a somewhat larger series of cases but could not confirm their findings.

Czerny and Eliasberger have attacked the problem from another point of view. They have taken a series of very emaciated tuberculous children (26) and have given them frequent injections (daily injections of from  $\frac{1}{2}$  to 1 c.c.) of horse serum. While the injections have no direct effect on the tuberculous process, 12 of the children showed a striking improvement in general condition. This effect on the nutrition and on the general condition of children has been reported by other observers as well.

**Tuberculous Meningitis.**—Hollis and Pardee call attention to the use of intraspinal injections of foreign protein (they used antimeningitis serum) in the treatment of tuberculous meningitis, reporting the recovery of 5 patients out of a series of 8. They regard the therapy as nonspecific, and call attention to the fact that the use of serum in the treatment of syphilis of the spinal cord—although combined with a specific drug—must also be regarded as a form of therapy based on the irritation of the meninges, with the therapeutic effect following as a result of the reaction.

Experimentally Baldwin and L'Esperance have noticed some increase in fibrosis in tuberculous guinea pigs after treatment with typhoid vaccine. Böhme, using a variety of nonspecific substances, vaccinurin, pus, influenza bacilli, streptococci and milk injections, could determine no alteration in the course of tuberculosis in the guinea pig.

#### TYPHUS FEVER

During the course of the war a number of investigators have had the opportunity of trying nonspecific therapeutic agents in typhus fever. These have included deuterio-albumose, salt solution, colloidal metals, convalescent serum and vaccines of various kinds.

Holler found that his method of therapy—daily injections of deuterio-albumose intravenously—was most efficacious in typhus when he was able to begin the treatment within the first two days after the onset; in that case he was frequently able to terminate the disease by crisis. When given later, while it shortened the course of the disease and had a pronounced effect in modifying toxicity, the results were not so striking.

In fifteen untreated cases the mortality was about 50%. In 50 treated cases only three patients died.

Equally favorable results have been described by Tagle, who began such therapy on the basis of Nolf's work, and by Opazo. Tagle applied the injections in 59 cases of typhus. Aside from one patient that died in less than forty-eight hours, the mortality was about 5 per cent. He declares that the absence of all ill effects

confirms the harmlessness of the method for all ages. The general health improves, the duration of the disease is shortened, and convalescence sets in earlier. The benefit was more pronounced the earlier the injections had been begun. His report represents extensive research by the different physicians on the hospital staff, much experimental and laboratory work being carried on preliminary to and during the clinical experiences. Nolf's technic was closely followed, except that the acidity of the solution of peptone in physiologic salt solution was reduced to 4.3 per thousand, and the remedy was put up in 5 c.c. capsules. About 10 c.c. was given as the first dose, to robust adults; otherwise from 4 or 5 c.c. For older children, up to 6 or 8 c.c. giving afterward only about half of the initial dose, and allowing an interval of forty-eight hours to elapse. In almost all the cases a second injection was given and, exceptionally, a third, with only 1 or 2 c.c. A subcutaneous injection of 2 or 3 c.c. of 20 or 25 per cent. camphorated oil was given every six hours day and night, with 0.25 c.c. of 1 per thousand epinephrin in each syringe. The patient must be kept in repose. The blood pressure falls during and immediately after the intravenous injection of peptone, but if it is made slowly (1 c.c. per minute) and if epinephrin has been given, the drop is slight. The coagulation time of the blood is much retarded. Analysis of the blood showed that the urea content could be disregarded with this protein therapy as the latter only slightly augmented it, and it soon dropped to below its previous figure from the rapid reaction to the injection, while the dietetic restrictions in typhus aid in its being speedily cast off. Analysis of the urine likewise showed that the injections of peptone had no detrimental influence on the kidneys and hence there were no contra-indications on the part of the kidneys, except, of course, with grave nephritis. There are no characteristic findings in the urine in typhus. The fever charts given show the attenuating and abbreviating influence of the protein therapy better than anything else. An interesting feature of the cases was that when the temperature had gone down under the injections, a further injection did not induce any appreciable reaction. The production of antitoxins can then be regarded as sufficient and the case as cured. In every case improvement in the general condition was unmistakable.

Opazo reports the application of Nolf's method in 27 cases of typhus, with 14 recoveries, 4 in convalescence and 7 still under treatment; 2 of the patients died, but the disease in their cases had reached a stage when reaction was no longer possible. He reiterates that the protein therapy induced a favorable reaction which modified the disease and all the symptoms. In his experience the reaction was prompter and more effectual in children than in adults. He is now applying this protein therapy as the routine in all cases of typhus.

Kalberlah reports good results from the intravenous injection of

typhoid vaccine. Bouygues has employed colloidal metals and Coglievina, who used dispartin—a colloidal silver preparation,—reports that the course of the disease was much less toxic and the mortality lower than in untreated cases. He gave on an average about 4 injections. Tietze used a 3% solution of collargol (5 c.c.) and noted a lessening of the toxicity.

The use of silver and antimony colloids has been suggested by Uhlenhuth and Frommes, but the number of cases treated by them has been too small to justify final conclusions.

Gyözi treated a number of cases with autoserotherapy and found that it seemed of decided benefit particularly in the older cases. Gudzent treated two cases with convalescent serum without apparent success. Raubitschek treated 25 cases with subcutaneous injections of normal horse serum. The mortality was about 6%. v. Zielinski used intravenous injections of the patient's own cerebrospinal fluid. In 20 severe cases 5 died. Munk has published a comparative study of the treatment of typhus with normal horse serum, peptone and with nucleohexyl. More recently Schultz, Charlton and Hatziewasilow have discussed a heterovaccine method which they claim has given good results. They used 2 loops of 48 hours' growth of typhoid organisms (killed at 60° C.) which were mixed with 5 c.c. of the patients' serum. This sensitized vaccine was then injected. A rather sharp reaction followed the injection but the clinical results seemed very satisfactory. In the series of 5 cases all recovered.

Perhaps a method that is equally successful is that described by Daniéopolu in his recent treatise on Typhus Fever. The author uses daily injections of hypotonic salt solution (0.065) which are given intravenously. In his untreated series the mortality was very great, in the treated fully 90% recovered.

#### VINCENT'S ANGINA

Capitan treated 200 cases of Vincent's angina with intramuscular injections of colloidal arsenic (6 c.c.). The cure was complete in from 24 to 48 hours. No local treatment was necessary. Stuhl reports a similar nonspecific method of therapy in using tuberculin in the treatment of Vincent's angina. While he treated but a small number of cases the results were quite striking.

## CHAPTER XII

### SPIROCHETAL AND PROTOZOAL INFECTIONS

#### RELAPSING FEVER

Bouygues reports that he has found the injection of colloidal metals useful in relapsing fever.

#### SYPHILIS

The fact that intercurrent diseases, particularly the acute infectious diseases, have a distinct effect on the manifestations of syphilis has been frequently observed by clinicians (Zehner). The effect may be apparent in delaying the onset of secondary eruptions or in hastening the involution of skin lesions already present. Neumann has discussed the subject quite thoroughly in Nothnagel's Special Pathology.

In view of the effect of temperature it was natural that with the study of protein therapy efforts would be made to determine what effects would be apparent on syphilitic skin lesions after nonspecific injections, and Biach as well as Kyrle, Weiss and Luithlen have described the involution of the skin lesions after protein therapy. Naturally the question is of greater theoretic than practical interest because we are fortunate in possessing much more efficient specific agents.

In the last two years considerable attention has been devoted to the study of silver preparations and their application in syphilis. The injection of colloidal silver has been found experimentally to prevent the proliferation of spirochetes in the tissues of rabbits (Kolle and Ritz) and silver preparations (collargol) have been used (see v. Notthafft) clinically with apparent success. Silver-salvarsan is not included in this category because its effect is of course essentially specific.

The effect of iodids should undoubtedly be included in the group of nonspecific agents because the mode of action in stimulating tissue autolysis (although by an indirect method, as demonstrated by Jobling and Petersen) is quite analogous. It is very probable that the nonspecific agents will have a place in the treatment of syphilis as adjuvants that permit us to make specific treatment more intense by facilitating the rapid distribution of the specific agent. Applications have been made of this theory by Schacherl, by Hauber and by Szedlack.

Schacherl has reported on the combined specific and nonspecific treatment of 10 syphilitic *neuro-arthropathies*. In these cases only one was temporarily cured, 5 showed some retrograde change, while 4 were unchanged.

In 16 cases of *cerebral lues*, the results were as follows: In 5 cases of hemoplegia, 1 was cured, 3 were improved. Five were of the disseminate type; of these 2 were cured, 3 improved. Three cases presented only eye symptoms. One of these was cured, one improved and one not changed.

Schacherl noticed that the Wassermann reaction was much more rapidly changed under the combined treatment than with mercurial treatment alone; it seemed very probable that the mercury was much more rapidly absorbed, because stomatitis was more frequently noted under the combined method than when mercury salicylate was given alone.

Stückgold, who has treated a number of cases of congenital lues with the milk "fever" therapy, rightly observes that one cannot expect to permanently cure syphilis by means of such therapy; all that one can expect is a remission of the disease manifestation. But he is convinced that the combination of the nonspecific reaction with specific agents is of particular value. He observed that with the combined therapy one required much smaller doses of the specific drugs to obtain therapeutic results and to influence the Wassermann reaction.

Schreiner used milk and peptone injections along with specific treatment in syphilis and found that the Wassermann reaction became negative much sooner in such cases than in those that were put solely on specific treatment. The effect on the Wassermann reaction has been studied by several observers after Uddgren called attention to the fact that in luetics a single injection of milk might render the serum positive (previously negative). Scherber found that in luetics an intercurrent febrile disease might have the same effect. In the therapy of syphilis by means of salvarsan the induction of an antianaphylactic state on the part of the patient has been found of value in preventing the occurrence of the salvarsan shock reaction. Bushman describes the method of Stokes, which consists of giving a preliminary dose of salvarsan ( $1/10$  the total dose); this is undoubtedly sufficient to cause an alteration in the permeability of the cells and so lessen the possibility of later intoxication. Mention has already been made of the fact that Jungmann used salvarsan interchangeably with serum in the treatment of scarlet fever.

#### WEIL'S DISEASE

A number of observers have reported that Weil's disease is favorably influenced by the injection of convalescent and normal serum (Heidenheim, Herbach, Mann; Kleinberger obtained no conclu-

sive results). Inasmuch as milk injections seem to be very active in influencing the liver (increase in thrombokinase, fibrinogen, shedding of glycogen, etc.) Döllken determined to use milk therapy in place of the serum—either normal or convalescent. The styptic effect of the milk injections might be expected to become manifest in the course of the disease. In one very severe and quite hopeless case he injected 3 c.c. of milk; the bleeding from the intestine ceased after five hours but the patient nevertheless died. In other less toxic cases Döllken observed a decided effect on the pigmentation of the skin. In several cases injected with albumoses and with milk there was practically a clearing of the jaundice in from 48 to 72 hours. A mild grade of jaundice persisted, however, in these cases despite further injections. The effect on the albuminuria was also quite marked, a single injection being sufficient to completely clear up the urinary findings. Döllken was not able to follow his cases for any length of time so that it is not possible to draw any positive conclusions from the work. There seems little doubt that nonspecific injections, particularly of milk, are able to effect the liver metabolism considerably and may so alter disease processes which have their principal effect in the liver parenchyma. Inada and his associates have also studied the effect of the injection of serum on the course of Weil's disease.

#### MALARIA

**Activation.**—The provocative effect of nonspecific injections has been made use of not only in activating latent gonococci, but also in cases of suspected malaria.

Thaller noticed that after milk injections in cases that were suspected of malarial infection the plasmodia could be demonstrated after the reaction in a certain number of cases. In thirty cases so injected 13 responded with the usual milk fever, in 12 a malarial type of fever was activated, in 5 there was no effect. Habetin used subcutaneous injections of nucleic acid to mobilize the plasmodia and Heese found that after nonspecific injections plasmodia could be demonstrated and paroxysms commenced one week after the injection. Schlesinger observed that malaria plasmodia were mobilized after typhoid inoculation; Freund also observed the activation of an old malaria after an intravenous typhoid injection, while Zupnik, v. Müller and Leiner report an interesting case of a double infection with typhoid and malaria in which the malarial paroxysms resulted in a typical nonspecific defervescence of the typhoid fever.

**Therapy.**—Silvestri would support the specific treatment of malaria with injections of foreign protein, serum, adrenalin, strychnin, etc., claiming that the combined treatment is better than when quinin is used alone. It is very possible that such measures may be useful

in facilitating the diffusion of the specific drug and getting more effect on latent foci of the plasmodia.

Schimert reports the treatment of some 70 cases of tropical malaria which had become refractory to quinin. These were chronic cases and in poor physical condition. He tried autoserotherapy and obtained a clinical recovery in 85% of the cases, that is, the patients were improved physically, gained in weight and were able to be at work, although the parasites were not altered by the treatment instituted.

## CHAPTER XIII

### MISCELLANEOUS DISEASES

#### ASTHMA

The recognition that asthma and hay fever were to be grouped among diseases due to sensitization of the patient in the nature of an anaphylaxis, has opened a series of exceedingly valuable and interesting investigative and clinical problems. Naturally the asthmas due to cardiac impairment or anatomical alterations resulting from tuberculosis cannot be included in such a category, but there is evidence accumulating that in this latter group of cases we must admit certain elements of sensitization. In Wolff Eisner's recent discussion one finds the admission that the tuberculous individual presents a definite hypersusceptibility to a number of proteins of nontuberculous origin so that asthmatic phenomena in tuberculous individuals are to be expected. So, too, in the true asthmatic we must expect that attacks will be precipitated not only by specific antigens but by a variety of metabolic alterations or shocks which may bring about focal activation such as has been discussed in the chapter of focal reactions. During pregnancy asthma may become manifest (Hepworth, Salaberry), although as a rule the reverse is more common—that is, asthmatics are usually free from attacks. Onset of attacks after remote trauma (Loeper and Codet) or psychic disturbances are common examples of the phenomenon.

As long as the conviction was entertained that desensitization was as specific as sensitization, efforts at therapy naturally centered about the determination of the particular protein that might be the cause of the disease and the endeavor to bring about an increased resistance or tolerance by subcutaneous injection of the antigen. Walker's publications in this field are of particular importance. Walker's method, which consists of desensitization by vaccination, is usually followed by quite satisfactory and often permanent results.

In recording observations on the treatment of asthmatics which were sensitive to various proteins and also those in whom no specific sensitization could be determined, Walker describes the therapeutic result in this latter group of 150 patients who were not sensitive to any protein with which they were tested. It may be well to quote Walker's observations in full:

"The following comparisons as regards treatment may be made between sensitive and nonsensitive asthmatic patients. In the previous article, which concerned patients sensitive to proteins, and in the

first part of this article which concerns patients sensitive to bacterial proteins, it was shown that in general a favorable prognosis could be anticipated irrespective of the age of onset of asthma or the age of the patient when treated. With the nonsensitive patients, however, the later the age of onset and the later the age of the patient when treatment is begun, the more unfavorable the prognosis. The duration of asthma alone played little part in the prognosis in either type of case. Seventy-five per cent. of the sensitive patients were relieved of asthma by treatment with the proteins to which they were sensitive, whereas only 40 per cent. of the nonsensitive patients were relieved of asthma by treatment with vaccines. The permanency of relief of asthma in the sensitive patients was of much longer duration than in the nonsensitive patients. Both the sensitive and the nonsensitive patients illustrate specificity in the treatment of bronchial asthma; that is, the specificity of proteins in the treatment of sensitive cases and the specificity of bacteria in the treatment of nonsensitive cases. We have, however, only inferred that nonsensitive asthmatic patients are not benefited by treatment with proteins. Because of the more or less general belief that infections may be alleviated by nonspecific protein therapy—and in the case of chronic arthritis this is frequently found to be true—it seems worth while to mention our results in the treatment of the infectious or nonsensitive type of bronchial asthma with proteins.

“Many of the nonsensitive or infectious type of asthmatics have been treated with various proteins. Three patients who were in the hospital wards because they were having severe asthma every day were given, intravenously, typhoid vaccine without improvement in the asthmatic symptoms. A week later a larger dose was given without any benefit. After this the patients were given, subcutaneously, two hundred million autogenous streptococcus vaccine made from their sputum in dextrose bouillon. A few days later one patient was somewhat improved, another seemed a little better and the third was not improved. A week later still the autogenous vaccine was increased to 250 million and a few days after this one patient was very much better, another was considerably improved and the third was somewhat better. The autogenous vaccine was given each week with gradual improvement in each instance until two patients left the hospital three weeks later and the third patient was able to leave in five weeks. Therefore, the intravenous typhoid vaccine was followed by no benefit, whereas the autogenous streptococcus vaccine was followed by a gradual though distinct improvement. Several of the nonsensitive summer asthmatics and some of the other nonsensitive cases were given courses of treatment with various pollen without benefit. A few nonsensitive patients were given wheat proteins and a few were given large doses of peptone subcutaneously without benefit. This latter method of treatment is dangerous unless the patient

is tested with peptone to rule out the possibility of his being sensitive to it. We feel that this fad of injecting patients with proteins to which they are not already sensitive is, in general, apt to be a mistake; the possibility of sensitizing patients to proteins, exclusive of typhoid vaccine, seems to outweigh the chance of improvement by such treatment."

On the basis of the fact that in antianaphylaxis (or desensitization) a nonspecific element is at times observed, other methods have been devised which are at times applied more easily than the specific methods that Walker has used. Only larger clinical experience will enable us to draw conclusions. It must be borne in mind, too, that our conception of protein therapy must not be limited to the intravenous injection of typhoid vaccine or peptone. Many of the milder reactions continued over a longer period of time may be found much more effective.

Auld has reported on the use of peptone injections (dissolved in physiological salt solution to which a small amount of sodium carbonate is added) given either intravenously or subcutaneously. This treatment has been instructive in respect of the grouping of asthmatic cases. Two main groups occur which show no tendency to pass into each other. One group comprises such as quickly respond to the treatment, and the effect is more or less lasting, the recurrences being infrequent and milder in character. The other group is resistant, and is subdivisible into such as are totally resistant and those in which, by careful immunization, the disease may be largely overcome. Pagniez and Widal, Abrami and Brissaud use peptone by mouth and Cordier uses peptone enemas. The peptone seems to be polyvalent for most of the substances causing the anaphylaxis. Some require the continuous use of the peptone; others do better when it is given for three to eight days followed by an interval of the same length. By this means they have succeeded in curing the tendency in time in many cases, the time required for complete desensitization depending, however, on the personal equation. Other observers have used colloidal metals and Boyd reported that he had successfully treated several cases of asthma with typhoid vaccine (50 million organisms intravenously). Danysz considers that the intestinal flora furnish the substrate for the antigen which sensitizes the patient in asthma, in certain skin and gastro-intestinal diseases. In an antiphylactic treatment he uses the bacteria isolated from the stool for subcutaneous injection with apparently good results.

Together with Miller we have used intravenous injections with typhoid vaccine in asthma in a number of cases. In some the results were quite satisfactory, in others there was no apparent effect on the attacks; the latter group including particularly the cases in which food sensitization was demonstrable. It is possible that a method such

as that of turpentine injections might be more satisfactory because the effect is prolonged over a considerable period of time.

Sterling has reported the use of nonspecific vegetable proteins in asthma; a number of observers have reported satisfactory results with endocrine glands of various types—ovarian substance (Fishberg), pituitrin (Bensaude and Hallion, Zueblin), as well as with normal horse serum (Zener) and the various antitoxins—diphtheria and tetanus. Danysz has discussed the general theory of antianaphylaxis or desensitization in a recent paper in connection with related diseases due to manifestations of hypersensitization in the skin and gastro-intestinal tract.

The indiscriminate use of sera of various kinds in asthmatics is a practice that should be discouraged because a number of deaths have been reported as a result of such injections. (Boughton.) It must be borne in mind that in this condition we are dealing with a patient highly sensitive to protein shock and great care should be exercised.

#### ANGIONEUROTIC EDEMA

Schulmann relates that discovery of a transient phase of hemolysis, the *crise hémoclasique*, in a number of cases of Quincke's disease has confirmed its analogy with other affections in which anaphylaxis is a factor, and treatment on this assumption is proving successful. He applies it in the form of autohemotherapy, drawing 2 c.c. of blood into a syringe from a vein at the bend of the elbow, and he reinjects the blood into the neighboring subcutaneous tissue, merely drawing the needle out of the vein and pointing the tip in another direction in the tissues of the arm. He has made hundreds of these injections and never had a mishap, but the desensitization may take up to two months, although there is relief almost from the first. Three typical cases are described; one woman of 31 had been subject to attacks of angioneurotic edema since before puberty, returning at different points and lately becoming more frequent and lasting for three or four days. She was given three injections a week and by the end of the third month the tendency seemed to have been arrested. She returns every three or four months to have a few injections of the kind made. In another case the attacks had been recurring every two or three days during the six months following a childbirth, and they were accompanied with headache and urticaria. There has been no recurrence during the year since the course of thirty-five injections.

#### SECONDARY ANEMIA

A number of observers claim to have obtained satisfactory stimulation of the hematopoietic system following nonspecific injection,

particularly milk, and have used it in the treatment of anemia. Thus Müller describes its use in the treatment of secondary anemia.

In *pernicious anemia* Grote obtained fair results with the injection of milk, one case increasing in blood count over 900,000 in a period of 8 days. As a rule he obtained little febrile reaction after the injections, contrary to the experiences of Schmidt in this class of cases. Müller claims to have had favorable results in bringing about remissions after milk injections (aolan) which increased the blood count and brought about an increased feeling of well being on the part of the patient.

Hollaender as well as Fischer reports some success with collargol injections. The effect is never a permanent one.

### HEMORRHAGIC DIATHESIS

Döllken has devoted considerable attention to the effect of non-specific therapy on blood diseases. That serum injections of various kinds have been found useful, indeed have in many instances been our only resource in the hemorrhagic diseases is, of course, well known and the literature is readily accessible so that it will not be necessary to enter into a discussion of it at this time. (P. Emile Weil, Chalier, Kurtz, Lewisohn, Berghausen, Know, Peterson.) \*

Döllken assumes that the bleeding in purpura is largely due to two factors—an increased fragility of the blood vessels and the alteration in the blood coagulability whereby it does not clot while in contact with the tissues. Perhaps when once shed the blood may show some delay in coagulation, but Klinger and others have denied this. Döllken considers the alteration in the platelet count as a symptom rather than a causative factor because in cases that have been long cured he has observed that the diminution in the platelet count may persist.

The leukocytosis of spontaneous fever, following vaccine injection, and following the intravenous injection of deuterio-albumose has practically no effect on the outcome or course of a purpura, the stimulation of the spleen and bone marrow that is involved seems insufficient to alter the disease process. (See also the paper of Radovici and Iagnov.)

On the other hand, milk injections seem to have a particular effect on the blood vessels of smaller caliber and on the coagulation

\*The effects of the serum injection are possibly due to the alterations in the amount of fibrinogen and thrombokinase that follow nonspecific injections of various kinds. Moll observed this increase and von den Velden, and Lowy have confirmed it for gelatin, serum, peptones and parenterally injected proteins in general. Moderakowski and Orator also studied the effect on fibrinogen and confirmed the previous workers. Wohlgemut has in a very recent paper demonstrated that the increase in fibrinogen probably results from liver stimulation, but that the thrombokinase arises elsewhere.

mechanism, the styptic effect being very apparent. Thrombokinase as well as fibrinogen are increased and the permeability of the capillaries altered, small doses seeming to increase the permeability, larger ones to diminish it.

Döllken therefore decided to use milk in cases of purpura and was surprised to observe the rapidity of the effect on the disease. He made injections of about 5 c.c. every three days, intramuscularly. There was little inconvenience; on the contrary, a marked euphoria was observed after the injections. In only one instance did a hematoma appear at the site of the injection and this disappeared after 24 hours.

Bleeding into the tissues stopped 5 hours after the injection, a most interesting feature being the observation that this clinical result was manifest without effect on the number of the blood platelets in the circulation. The permeability of the vessels does not seem to be altered as rapidly as the effect on the coagulation mechanism, because small petechiæ were noted to appear until about 24 hours after the injection.

The resorption of blood from the tissues commenced promptly after the alterations in coagulation had taken place. After from 7 to 8 hours small hemorrhages in the mucous membranes of the mouth could be observed to be decreasing in size; in another 8 to 10 hours the smaller ones had disappeared and the larger areas showed considerable retrogressive change. Large areas of bleeding showed a broad yellow band of discoloration from 1 to 2 c.c. wide around the margin in from 18 to 24 hours where regression had occurred, and the tension of the hematomas was lessened.

Döllken details his experience in one severe case of purpura. The patient bled two hours from a small skin abrasion, and the bleeding recommenced on the slightest renewed trauma to the scab. The paraffined blood coagulated in 9 minutes. Deutero-albumose (.05 gm. intravenously) merely increased the bleeding that had occurred from a small skin puncture from the ear for several days. The following day a puncture still bled for 14 hours; the paraffined blood coagulated in 14 minutes. During this time numerous fresh areas of hemorrhage had been observed over the body. The patient was then given 5 c.c. milk intramuscularly. In 5 hours all bleeding ceased. After 8 hours the petechiæ in the mucous membrane of the mouth were decreasing in size. Bleeding from a new skin puncture in the ear lobe now ceased in 20 minutes and the paraffined blood coagulated in 8½ minutes. Platelets were absent during the entire clinical change. Leukocytosis was moderate. All cases that had albuminuria beforehand showed clear, albumin-free urine after the injections.

Bosanyi has found that intravenous injections of salt solution have given him results that are more satisfactory in purpura simplex, morbus Werlhofii and hemophilia than any other method that he had

employed. He describes the result obtained in 7 cases, the first two of which received injections of 5 c.c. of 3% salt solution. Later he used larger doses (about 10 c.c. of a 5% solution) and with these the results were striking. The bleeding usually ceased after a few hours. Injections, given daily, were without reaction on the part of the patient. He is under the impression that the result on coagulation is due to the reversal of the exchange between the capillaries and tissues so that there is an actual imbibition of "tissue fluid" and coagulating accelerating substances from the tissues by the blood stream, based on the work of von den Velden.

Vines would effect hemorrhagic conditions by means of anaphylactic shock effects or sensitization. Vines bases his method on the following considerations:

The intradermal reaction is a modified form of anaphylactic shock of general as well as of local significance, in which the stimulation of the thrombogenic functions of the somatic cells is a salient feature. The changes in coagulability of the blood in anaphylactic shock occur in two stages: a period of acceleration which occurs early, followed by a period of retardation; further, that the predominance of the former or the latter depends on the lesser or greater severity of the shock. The intoxicating injection in a sensitized individual may act as a catalytic agent in inducing the intracellular reactions which constitute the anaphylactic phenomena. In cases of hemophilia, Vines says, the duration of the effect of the intradermal reaction is dependent on the duration of the anaphylactic period. But the shorter or longer duration of this effect is also directly dependent on the greater or lesser severity of the hemophilic condition.

He describes 3 cases so treated, all being sensitized to sheep serum and small doses of sheep serum injected interdermally after sensitization. In the first two cases the second injection caused an increase in the blood clotting rate of the individual, which was evidently quite permanent, in the third case the effect was less apparent. Confirming Vines' observations, Rouchetti reports two severe cases of hemorrhagic purpura which abruptly subsided when serum sickness, with urticaria, followed an injection by the vein of normal horse serum or of serum from the emulgent vein of goats. A similar method to stop bleeding after operation has been used by Neirotti and Viola. Neirotti and Viola report two cases of persisting hemorrhages after a minor operation, finally arrested by the anaphylactic shock from the subcutaneous injection of normal horse serum, eighteen hours after a preliminary injection of 10 c.c.

Voight treated several cases of *scurvy* with milk injections and noted a prompt styptic effect, as well as general improvement of the patients.

## NEPHRITIS

The albuminuria that accompanies many acute febrile diseases is very promptly influenced by nonspecific injections, according to a number of observers.

Treatment of a case of *pyelonephritis* has been reported by Gow, who in this instance made use of a colon-like organism for intravenous injections. A chill was invariably produced in about 3 to 3½ hours; there were nausea and headache and the temperature rise usually went to 103° F. or 104° F. This organism was at first used in a dosage of 50; later 75 and 125 million were injected but the severity of the reaction diminished with successive injections. Thus when the dosage of 75 million was injected the reaction was only to 101.6° F. with some cutaneous hyperesthesia and yawning on the part of the patient. This case of *pyelonephrosis* made a complete recovery.

In colon and *staphylococcus* pyelitis with concomitant bladder irritation Karo has reported very favorable results with injections of terpichin. Similarly in *staphylococcus* infections of the urinary tract and in the *cholecystitis* of children the results have been satisfactory. In cases of simple bacteriuria, however, no results were obtained. In the *cystitis* that accompanies enlarged prostate glands the injections were also found useful.

## NEURITIS

Döllken has prepared an autolysate of *staphylococci* and *bacillus prodigiosus* which has been used rather extensively and is distributed commercially under the name of "vaccinurin." Döllken tried out a series of bacterial extracts, including tuberculin, and vaccines in neuritis and concluded that the combination above mentioned was followed by the best results. From his work he was led to the belief that in heterovaccination we do not deal wholly with a nonspecific plasmaactivation but that there existed a degree of selectivity in the effect of the different vaccines, that is, they were more or less organotropic.

In the first series of neuritic processes (51 cases) treated by him are included both trigeminal and intercostal neuralgia, sciatica, and a large number of neuritides of varying etiology—cold, professional, alcoholic, post-typhoidal, luetic, diphtheritic, pressure, facial and radial. He observes that the pressure neuralgias and the so-called rheumatic palsies were the ones most easily influenced.

Holtzl reports the treatment of some 90 cases with vaccinurin. Of these 61 made complete recoveries and 28 were improved. The series included 25 cases of sciatica of whom 16 made prompt and complete recoveries. The injection was followed by a systemic effect and

the maximum therapeutic effect was observed in about 6 hours after the injection.

Cadbury has described the results obtained with typhoid vaccines in a group of cases with neuritic pains due to a variety of causes. These included one carcinoma of the breast, in which there was temporary relief from pain; four gunshot injuries, all of which were cured; one fibroid phthisis which was relieved, 1 tic douloureux which was improved for 6 months, etc.

Boyd also reports the successful treatment of neuritis with moderate doses of typhoid vaccine intravenously.

Following nonspecific injections in neuritides a distinct focal reaction may become manifest. There may be a transient increase in the pain and other manifestations of the lesion that reaches its maximum in from 4-8 hours, depending on the method used to elicit the reaction, followed by an analgesia which in some instances may be transient, in others permanent in character.

Wishura using "vaccinurin" found that neither the focal nor the general reactions were very severe. In severe degenerative inflammation of nerve trunks as well as in the more common joint neuroses the injections were very successful.

#### EAR AFFECTIONS

Rauch reports the results of milk injections (5 c.c) in 41 cases of acute middle ear infections. According to his series the results were very favorable, only three of the cases requiring operative interference. Gomperz, on the other hand, obtained no satisfactory results and Hirsch, who used turpentine injections in cases of furunculosis and eczema of the meatus, as well as in acute and chronic suppurative conditions of the ear, obtained entirely negative results.

The first report on the subject was that of Alexander, who has described his results in ear diseases and sinus infections; later Lawner reported some cases of middle ear disease treated with milk injections with excellent results.

#### MALIGNANT NEOPLASMS

A number of procedures and "cures" for both carcinoma and sarcoma have been advocated during the course of more recent years which have had as the basis of their mechanism the alterations which we now recognize as due to nonspecific stimulation. I need but recall the treatment of cancer with trypsin and amylopsin injections by Beard and the treatment of sarcoma by the injection of Coley's fluid, a bacterial autolysate; or the use of tumor autolysates or serum (Lewin) for purposes of immunization. These and all other methods that provoke a similar systemic response are followed by one of two reactions on the part of the patient.

When the tumor is small, not necrotic or ulcerated, there may result little or no temperature reaction or malaise following the injection and relatively little local effect. There may be a slight increase in pain at the focus and some evidence of an increased inflammatory reaction, but the size of the tumor will not alter materially. Indeed at times the rate of growth is increased.

When we deal with a large tumor mass, with either central necrosis or ulceration, nonspecific injections are as a rule followed by a decided rise in the temperature and a feeling of malaise. The further course will be determined by the effect on the local pathology. There is usually a marked increase in the pain and evidence of inflammation, digestion takes place of the necrotic material and the tumor may become apparently smaller in size. The general condition of the patient at this time will vary with the amount of the protein split products which are absorbed. If large in amount and but partially digested, the temperature will continue high for a period of several days; if small in amount, or if more completely digested at the focus before absorption, then the temperature reaction may fall within the limits of the provocative temperature of the nonspecific agent injected. In either case, in the period of recovery from the nonspecific reaction and from the reaction caused by the absorption of the autolytic tumor products, the balance swings to the reparative side and a general euphoria with increased appetite, lessened pain and irritability, improved nutrition and feeling of strength may set in which will last for a variable period. If a diminution of the size of the tumor (because of the digestion of necrotic material) has occurred at the same time, the natural inference of curative effects are prone to further encourage both the patient and the physician. This clinical reaction has been the basis of practically all of the methods of therapy which have at various and sundry times been reported and it is quite possible that it takes a part in the reaction that follows after Roentgen and radium treatment, although by no means must it be held accountable for all the effect there achieved.

We cannot avoid the conclusion that the nonspecific reaction has little or no effect on the rate of growth of the malignant tissue as long as it is well supplied with vascular connections. Once the tumor cells become necrotic or perhaps undergo some of the earlier degenerative changes, digestive stimulation such as that which follows nonspecific therapy has an apparent effect similar in character and range to that observed in other pathological conditions.

On repeated injections the effect becomes less manifest and the reaction usually less severe, depending, of course, on the amount of necrosis present in the tumor. One finds that not only the commonly used nonspecific agents, but even iodine injections are followed by alterations in the tumor and a febrile reaction due to focal digestion. Moresowa has demonstrated this fact in a series of cases.

The recent experimental work of Murphy and others dealing with the lymphocyte as a factor in resistance to malignant infiltration is one that is not involved in the nonspecific reaction here described because the lymphocytic reaction after such injections is negligible. Müller has, however, called attention to the fact that epithelial tissues—he observed new formed epithelial bridges covering granulation tissue—seemed particularly susceptible to the digestive changes induced by milk injections, etc.

A different course of procedure has been adopted by Opitz and Friederich in trying to use the nonspecific reaction in conjunction with the Roentgen irradiation. While their result is merely experimental, it offers at least the possibility of development.

In their studies on the treatment of carcinoma by means of Roentgen irradiation and radium they soon came to realize that the growth does not depend wholly on the inherent rate of the tumor cell growth but on the resistance of the tissues that were the seat of the malignant invasion. This varies not only with individuals but under certain physiological conditions as well. v. Groff, as well as Slye, have, for instance, called attention to the depression of the rate of tumor growth in mice during pregnancy, and while Slye seems to consider the increased metabolic demands of the maternal and fetal organisms responsible for this inhibition on the rate of tumor growth, other factors possibly enter into the mechanism.

A similar depression in the rate of growth may be observed at times during the course of infectious diseases, after serum injections and other related procedures where we find an increase in the anti-ferment of the serum and a resulting tendency for the protection of connective tissue and a depression of the protein metabolism that follows after all these nonspecific alterations. Of course, during the acute shock effects—either in infectious diseases or after nonspecific injections, or after parturition—when proteolytic enzymes are mobilized, marked digestive phenomena may be observed at the site of the malignant invasions but this usually concerns the digestion of tissue already necrotic, or of connective tissue hyperplasias.

Bergel has reported observations concerning the acceleration growth of bony tissue after nonspecific injections and Hoke, Doberauer and Pittroff saw a similar effect on connective tissue. Opitz and Friederich proceeded to make use of this principle in their work with Roentgen rays. Assuming that after irradiation the connective tissue cells were to a degree fatigued, by nonspecific injections these cells might be stimulated and the fatigue so overcome. On this basis these rejuvenated cells would then react like young cells and an atreptic immunity would be established; the carcinoma cells would die of inanition, would be “strangulated” and become necrotic.

While their results are not extended enough to warrant any conclusions they state that they were encouraging. Warnekros is said

to have combined serum injections with Roentgen rays in a similar manner of treatment.

## PEDIATRICS

Slawik has reported on the treatment of infants with nonspecific therapy, using human milk injected intramuscularly in doses from 1 to 5 c.c. usually in two-day intervals. In most cases the milk was first boiled; in a few cases he used the raw milk without encountering any ill effects.

Slawik found that the reaction obtained was independent of the age of the child, but was influenced by the state of nutrition, that is, the vitality of the patient, by the feeding, and to some extent by the particular disease process from which the child was suffering. There were no ill effects from the injections and when for purposes of comparison healthy infants were treated with injections of similar amounts there was no alteration in the weight curve. With repeated injections the reactions became less intense and Slawik calls attention to the well-known fact that humans are normally relatively resistant to anaphylactic sensitization so that the danger from this source should not be overestimated.

Among the 26 cases treated by him were the following:

3 ophthalmoblennorrhoea. These were followed by a decided focal reaction; one improved at once, the others after repeated injections.

3 erysipelas. 1 improved at once, one after three weeks, the other case became chronic and later developed meningitis.

4 of multiple abscesses. These were healed in from 7 to 10 days.

1 phlegmon in a marantic child. The general condition improved after the injections and, despite the continued cachexia, the phlegmon healed.

2 marantic infants. One of these with thrush; this infant became more agile, drank better and recovered. The other was not altered.

3 with chronic exudative diathesis; they were not altered.

6 severe dysenteries, of whom 4 died. After the injections a very high agglutinin titer was observed in all the cases.

In a later series Slawik injected infants parenterally with white of egg, breast milk or other substances in treatment of various pathologic conditions. The results were disappointing, probably on account of the inadequate development of the defensive forces at this age. Actual benefit was realized only with pyodermitis and gonococcus infection.

Langer has studied particularly the furunculosis of infants. He noted that after the injection of various vaccines, no matter what the clinical result, there was little or no antibody response. As a result he decided that the clinical benefit could not be a specific one

and that he might just as well discard the old idea of a negative phase and the interval dosage as formerly used. He therefore gave large doses (500 to 1,000 million) of staphylococcus vaccine (opsonogen) intramuscularly. Injections were made daily, usually two or three injections sufficing to bring the disease process to a standstill and the recovery of the patient usually followed in a short time. Whenever phlegmons existed they were of course opened and drained.

The vulvovaginitis of infants and children does not yield to non-specific therapy (collargol—Vollbrandt).

Normal horse serum has been used successfully as a stimulant in poorly developed infants by Ferreira. It seems to whip up the sluggish metabolism and nutrition in general so that the child afterward progresses more or less normally. He injected it in three cases here described. One of the infants weighed only 3,750 gm. at the tenth month when the serotherapy was started, and the benefit was so unmistakable that it was kept up for sixteen months, the child having thus been given 2,386 gm. of the serum, and its weight showing a regular increase. He began with 2.5 c.c. but soon reached the dose of 20 c.c., repeated two or three times a week. A 3 months' babe improved so rapidly after the serotherapy was begun that the latter could soon be dropped, the improvement continuing thereafter. None of the three infants was entirely breast fed. Rinz has reported similar cases.

Czerny and Eliasberg have used this effect of nonspecific therapy to stimulate the general condition of children ill with tuberculosis. In 26 cases so treated (daily injections of normal horse serum in doses up to 2 c.c.) 9 died; in 12 there was remarkable improvement despite the fact that some of the cases were tuberculosis of the peritoneum and of the lungs.

Valagussa has made a careful study of protein therapy in acute diseases in children and in his report reproduces the temperature curves of the various groups treated with different proteins. In 51 children from 14 months to 12 years old, all with typhoid fever, the intramuscular injection of peptone according to Nolf had a very favorable influence on the course of the disease in the majority. In 31 cases of influenza in children, he injected various serums and anti-serums, and when this serotherapy was early, intense and continued, the results were excellent. There were only 3 deaths in this group of 31 severe cases of influenza. His experimental research on the autolysates of beer yeast in colloidal suspension confirmed their efficacy in increasing opsonins, etc., and this was sustained in 33 cases of pneumonia or typhoid while no effect was apparent in 3 cases of whooping cough.

The three types of antigens represented by peptone, horse serum and organized ferments behave alike; the only difference is in the intensity of the phenomena induced. The yeast autolysates are the

weakest and slowest in their action, but all serve to reënforce the organism in its fight against the infection. There are no symptoms of anaphylaxis with the yeast, aside from the local reaction, and the effect on the temperature, and he commends this as a harmless means to activate and augment the kataphylactic powers of the organism in any and every bacterial infection. "With this extract of the cells of the saccharomyces we provide a poly-antigen therapy, and we cannot go amiss in treating a disease by augmenting the natural index of resistance and the defensive forces."

The largest series of infants has been treated by Plantenga (300 cases). These included various marantic infants, usually with alimentary intoxication. He injected as a rule some 30 c.c of an "anti-colon" serum obtained by immunizing animals against colon bacilli. The results were quite remarkable.

More recently Putzig has also described a number of cases. He found that serum injections (he used diphtheria antitoxin) in marantic children caused an increase in weight and an improvement in the general condition and that this improvement was not a temporary affair (due to water retention, etc.), but was due to a stimulation of the body tissues and an actual growth of tissues. Of 7 cases 5 were appreciably improved.

## CHAPTER XIV

### TREATMENT OF GENERAL PARALYSIS, TABES, ETC.

While the etiological significance of the *Spirocheta pallida* in its relation to tabes and general paralysis has been firmly established, the therapy of these diseases has never been very satisfactory, despite the development of our more intensive methods of mercurial treatment and the intravenous and intraspinal application of salvarsan. The damage once done the central nervous system is irreparable and the problem of therapy resolves itself largely in preventing progress of the disease rather than with the thought of recovery. Even this modest result is seldom achieved. Remissions are of course known to occur spontaneously during the course of the disease and this fact is more often than not apt to bias the observer working with some new preparation and he ascribes therapeutic effects to the procedure which are not actually due to the remedy.

#### GENERAL PARALYSIS

There seems little doubt of the clinical observation that has been made by numerous observers and for many years that intercurrent infections (malaria, typhoid, suppurative processes, etc.) are not uncommonly followed by an arrest of the disease process and even apparent improvement in the general condition of the patient suffering from progressive paralysis (v. Halban, Marro and Ruata, etc.).

Very early efforts to make use of this knowledge were reported. Jacobi in 1854 reported on the use of artificial abscesses in the treatment of general paralysis and Meyer in 1877 again took up the method.

Some rather illuminating statistics have been compiled by Mat-  
tauschek and Pilez in this connection. They found that in 4,134 cases of syphilis 4.7% developed general paralysis. In a group of 157 of the luetic cases there was a history of an intercurrent infection such as erysipelas, pneumonia, etc.; not a single case of general paralysis developed among these. While by no means free from criticism, they nevertheless confirm to some extent the clinical observations just alluded to.

It was on this basis that v. Jauregg began the use of tuberculin in the treatment of general paralysis; tuberculin being selected as a pyrogenic agent because of its availability and the certainty of the febrile reaction. v. Jauregg had first tried a pyocyaneus vaccine in

a series of acute psychoses with results that encouraged him to extend his experiments to other forms of mental disease. His associate, Boeck, has published the results of the treatment of cases of general paralysis in v. Jauregg's clinic.

Pilcz continued the method. He gave old tuberculin in 10% solution, starting the treatment with 0.01 gm., and continuing up to 0.5 gm. Injections were made every two days. The patients reacted with a temperature up to about 101° F. and there was an associated headache and lassitude. Pilcz noted that at times there was an increase in the psychic disturbance at the time of the reaction, but this usually rapidly disappeared.

In contrasting a series of 66 treated cases with 66 not treated the mortality was 20 and 39 respectively during the first year under observation. At the end of a four-year period of observation 8 of the treated group were still living, 5 of the untreated.

In 1911 Pilcz published a further series of 86 cases, which were given a combined treatment of potassium iodid and tuberculin.

Of these 40% did not respond to treatment;  
 23% were arrested, but not otherwise improved;  
 10% became fit to be returned to normal life; and  
 26% were restored to almost normal condition.

In 1912 a further report was made. At this time 26 were still living, 12 of them occupationally fit, the periods of remission in 3 cases having lasted for from 4 to 5 years, in 15 cases over 1 year.

These observers used tuberculin because it was convenient to obtain and sure in its effect. They observed that patients who seemed hypersensitive to tuberculin and reacted violently were those who derived the greatest therapeutic benefit from the method.

Hudovernig, Battistessa, Döllken, Jukow and Joachim confirmed these findings.

The basic theory of v. Jauregg was that the therapeutic effect in paresis was due to the increased temperature. The work of Jahnel and Weichbrodt—who found that in luetic rabbits subjected several times to temperatures of from 42° to 43° C. living *spirocheta pallida* could no longer be found (other spirochetes were not so susceptible to high temperatures)—is of particular interest in this connection. Donath had previously used salt injections, and now, with other neurologists, began the treatment of general paralysis with leukocytic stimulants, considering the leukocytosis thereby obtained as the important factor of benefit to the patient. Horbaczewski having called attention in the early nineties that nucleic acid (as well as pilocarpin and cinnamic acid) acted as powerful leukocytic stimulants, nucleins were applied by Fisher and by Donath in the treatment of general paralysis.

Fisher's first series contained 22 cases so treated and 22 untreated

cases as controls. The treatment consisted of injections of one-half gram nuclein in 10% solution. The average duration of life of the treated cases was 15 months, of the untreated 7 months. Later he treated a further series, this time with larger doses—from ½ to 3 gm. in 10% solution every 3 to 5 days. Of these ten were treated, ten untreated. The treated cases gave 5 remissions (three becoming progressively active again). In the ten control cases there was but one remission, that following a long continued septic condition.

Donath treated 21 cases with injections every 5 or 7 days, each injection resulting in a febrile reaction that lasted for one or two days. On an average 8 injections were given the patients; the leukocytic reaction was quite marked, up to 61,000 in one case. Of these cases 70% showed definite evidence of improvement—in 47% the improvement was so great that they became self-supporting. He noted that the tremor decreased, excitement diminished, there was an improvement in memory and in mental agility. The longest period of remission initiated by the therapy was 3 years.

In a second series of 15, 9 showed definite improvement, of whom 3 were able to again become self-supporting.

Hauber gave a combined antiluetic and nonspecific treatment to 36 patients. Of these 13 improved, but 23 showed no evidence of therapeutic effect.

Szedlák treated 25 patients simply with the nucleic acid and an equal number with nucleic acid and mercury with the following results:

	Nuc. alone.	Nuc. and Hg.
Marked improvement .....	8%	40%
Slight improvement .....	24%	24%
No improvement .....	31%	16%
Interrupted treatment .....	4%	4%
Died .....	33%	16%

In a more recent paper v. Jauregg reported the treatment of 33 cases with staphylococcus vaccine in lieu of tuberculin formerly used. In this series 61% improved, 10 of the patients being restored to almost normal health. v. Economo reported similar results. Schacherl treated 38 cases of general paralysis (ambulatory) with a combined course of tuberculin and mercury. Of these 13 continued the course to completion. Seven of these were much improved, 5 of them were again enabled to earn their living. One developed a phlegmon after a severe eczema; this patient became lucid and was permanently cured.

Of course these favorable results have not been allowed to stand unchallenged. Hüssels, Lépine, Jolowicz, Plange and Hoppe failed to find any therapeutic benefit from the use of tuberculin or the nucleins when injected. Lowenstein and Kleinberger have indeed claimed that the injections have done actual harm. Bouman, who used tuberculin,

nucleinate and salvarsan, got very little results with any of them, the effect obtained being at the most transient.

Brown and Ross have discussed this treatment of mental diseases by the production of leukocytosis, treating 9 cases by means of nuclein injections. There was not much mental improvement despite the fact that a leukocytosis of from 17,000 to 20,000 was obtained in many cases.

Bruce has reported on the use of turpentine and sodium cinnamate, and collargol has also been tried by Vergueira in a dose of from 5 to 10 c.c. of a 1% solution.

Friedländer has used intravenous typhoid injections; Plaut tried out the effect of injections of streptococcus and of staphylococcus vaccines without apparent results; the leukocytic response was of low grade. Recently v. Jauregg has even suggested the infection of the patient with malaria plasmodia to keep up a febrile reaction at definite intervals. Weichbrodt and Jahnel report on a number of cases so treated and Mühlens, Weygandt, and Kirschbaum have recently reported on a series of 33 cases treated by infecting the patients with the spirillum of Obermeier and malaria plasmodia. Of their series 12 were of such recent date that the end result could not be properly judged. Of the remaining 21, 4 cases died (not directly from the infection), while 12 were markedly improved, with remissions persisting for a considerable time. The papers by Steiner and Pagniez are also of interest in the same connection. A review of the entire subject will be found in articles by Enge and by Raecke.

We are perhaps justified in assuming that the work of the Vienna school in this particular field may offer some advance in our methods of therapy which, at best, are none too satisfactory. That intercurrent infections affect the degenerative process or at least the rate of destruction is very likely from what we know of their effect on other pathological conditions, and there is no reason why the various nonspecific procedures suggested may not at times be followed by some clinical improvement. It seems possible that in a combined ergotropic and etiotropic method some dependable results may yet be achieved.

#### TABES

Döllken has treated some cases of tabes, but a larger series has been reported by Schacherl. Schacherl used a combined specific and nonspecific method of therapy, beginning with 0.001 gr. of tuberculin and then giving 0.1 gm. of salicylate of mercury with each third dose of tuberculin. He observed that early in the course of treatment, i.e., when the patient had considerable reaction from the tuberculin, the effect of the mercury was also much more in evidence, salivation being noted much more frequently.

With this method of treatment the results in 76 cases, with one

exception, were very good. At times an initial intensification of the disease symptoms was observed with the beginning of the treatment, but later this subsided. While the ataxia was not much altered, an increase in the rapidity of transmission of sensory stimuli was apparent in all cases and the ability of the patient to work was greatly enhanced.

An analysis of the results of treatment of the 76 cases follows:

53 were of the ataxic type—36 were much improved, 17 were slightly improved in walking.

46 suffered from lancinating pains—38 of these were cured, 5 were improved.

24 gastric crises—of these 23 were cured.

25 had bladder symptoms—12 were cured, 11 improved.

Miller is said to have observed that the lancinating pain disappeared after milk injections (Boas). Wodak treated a number of tabetics with tuberculin and found that the patellar reflex was restored in several of his patients after the treatment. Friedländer is said to have obtained a similar result.

It is to be remembered in this connection that while we may at times improve the symptoms existing in the tabetic, at other times a nonspecific injection may precipitate a gastric crisis or lancinating pains. Schmidt indeed calls attention to this possibility as a manifestation of the focal activation so frequently observed following nonspecific injections.

Itten tried nonspecific therapy in the treatment of *dementia præcox*, treating a series of 9 cases with injections of a 2% solution of nuclein (giving from 0.5 to 1.4 gm.). The cases were not improved. Döllken has treated 21 cases of whom 16 temporarily improved following injections of pyocyaneus and dysentery vaccines.

#### EPILEPSY

A number of procedures, essentially nonspecific in character, have been tried in the treatment of epilepsy, beginning with the use of serum injections by Ceni in 1903, brain extract by Lion in 1911, cerebrospinal fluid by Gordon in 1914 and immune rabbit serum by Held. Turner treated 23 cases with colloidal platinum injections and noted a diminution in the number and intensity of the attacks.

More recently two interesting reports have been published by Döllken and by Edgeworth.

Döllken used a combined milk and luminal therapy; to the milk injections he added a small amount of vaccine (nonvirulent organisms) and injections were usually given twice a week; after therapeutic improvement took place the number of injections were decreased.

Twelve cases were free from attacks for a period of 18 months, 60 for one year. As a rule from 4 to 6 months were required for treatment. In 13 cases the result was not a complete cure, but merely an improvement.

Edgeworth's series was smaller and the course of treatment shorter.

In the series of twenty-three cases a 5 per cent. solution of peptone was used, made up according to the prescription of Auld. It was injected. If a fortnight went by without the occurrence of an attack was 5 minims. In succeeding weeks 7, 10, 15 and 20 minims were given unless toxic symptoms occurred. No dose greater than 20 minims was injected. If a fortnight went by without the occurrence of an attack, the dose was not further increased. If no results were obtained after three doses of 20 minims the treatment was given up. In four cases toxic symptoms were observed, rigor, vomiting, temporary pyrexia, either as an isolated phenomenon, or in any combination. If this happened, the next dose was lessened. In such cases it was found that the dose could be increased later to the old figure or even beyond without the occurrence of any untoward symptoms. In three cases of posthemiplegic epilepsy no improvement occurred. In eleven cases of epilepsy without signs of any gross cerebral lesion no permanent arrest was produced. In four of these the fits ceased but subsequently recurred, though in lessened severity, and in two cases the frequency was lessened. The average age of the patients was 18 years, the average duration of the disease ten years, and the average frequency of attacks, once a week. In nine cases of epilepsy without physical signs of any gross cerebral lesion the attacks ceased. This arrest has now lasted more than a month in all cases, and in some as long as three months. Five of the patients were mentally defective—in one of these cases no mental improvement occurred, in three some improvement, and in one considerable improvement was noted. The average number of injections given was five and one-half.

Geyelin has recently reported that fasting may at times be followed by the cure of epilepsy. Whether the therapeutic effect is dependent on the acidosis involved in the method, and thereby related to other nonspecific shock effects, has not been established.

## CHAPTER XV

### SKIN DISEASES

"To treat skin disease wholly from without," Ravaut has recently declared, "is as irrational as treating the skin lesions of syphilis by local applications alone. And yet the dermatologist is too apt to focus his attention exclusively on the local process. He must be a biologist, not a mere botanist." While Ravaut's statement is rather broad, there is nevertheless much value in the emphasis that he places on the fact that the dermatologist, as the result of more recent work in the general pathology and physiology of the skin, must not be satisfied with a purely local conception of the pathology or the therapy of the particular disease that may be under consideration.

Not only must we consider the fact that general systemic reactions can profoundly alter the reactivity of the skin—both enhancing or retarding inflammatory processes—but we must take cognizance of the fact that the integument seems to respond to bacterial invasion or protein injection, perhaps even to other chemical or physical agents with an allergy, an alteration in reactivity which is the more remarkable in that it seems to be a definitely localized phenomenon, an acquired property of the individual cell. This allergy, once established, may be transplanted if the cell is transplanted, but the general organism need take no part in the alteration whatsoever.

Equally interesting is the effect of the stimulation of skin metabolism and the effect on systemic diseases, as Heims has indicated and as Bloch and Hoffman have discussed at greater length. These have, however, been discussed in another chapter.

During the past two decades a considerable number of observations concerning the effects of systemic alterations on skin diseases have been gathered, but even previously one finds isolated records that are of particular interest. One needs but recall the observation that a variety of drugs—thyophen, benzol, acetone, taurin and amines (Spiegler), atoxyl (Moro and Steeman), cantharidic acids and salts (Liebreich)—would, when injected, cause a reaction at a lupus focus; that dietary faults aggravate an eczema; that intercurrent infections would favorably influence a preëxisting skin lesion (Restrepo has but recently reported such a case) or that yeast therapy might influence a furunculosis.

Skin diseases have afforded particularly favorable material for

treatment by vaccines, and the treatment of acne and of furunculosis became more or less the special field of the vaccinotherapist. Sero-logical procedures, too, such as that of autoserotherapy in psoriasis, have had their advocates. The fact that the results could be judged quite objectively has made this field one of interest and value.

Linser in working with the dermatoses of pregnancy found that the injection of serum (normal) was at times followed by marked improvement and the application was extended to urticaria, purpuras, strophulus, pruritus and related conditions where vascular alterations might be surmised as the basis of the pathology. Zieler, Bingel, Henck, Lowenberg and others have reported results that were confirmatory. Later psoriasis came to be selected for treatment of this kind and a number of American observers have reported their observations with this method of therapy. (Lit. by Luithlen.)

Quite a number of nonspecific procedures have been applied in the therapeutics of skin diseases in recent years. The use of autogenous serum injections in psoriasis was occasionally followed by a degree of improvement, although the method was too cumbersome to come into popular use. Perry, however, substituted normal horse serum for autogenous serum with satisfactory results. From 6 to 9 injections were necessary to produce therapeutic effects.

Milk injections were used shortly after their introduction by Schmidt and others. That tuberculin would cause the secondary lesions of syphilis to undergo involution was reported by Blach, while Scholz has discussed the fact that tuberculosis of the skin reacts to injections of trichophytin as well as to a variety of other substances. Engmann and McGarry began the use of typhoid vaccine in the treatment of a variety of skin diseases, among them a few syphilids, exfoliative dermatitis, lupus erythematosus and psoriasis. Engmann and McGarry made use of typhoid vaccine in dosage of from 75 to 500 million.

Scully in 1917 reported on the treatment of several cases of psoriasis with injections of typhoid vaccine, 8 cases being treated with injections varying from 75 to 100 million organisms. The results were not very satisfactory; Scully noted that the effect of the injections on the temperature and leukocyte curve was not as marked in these skin cases as it had been in the cases of arthritis treated by him. Rezende's reports show the prompt and radical cure of extensive psoriasis under "protein shock" treatment. It was in the form of 20 c.c. of normal horse serum, injected into the abdominal wall. An injection of 10 c.c. two days before had not induced an appreciable reaction, but the 20 c.c. caused fever for five days, reaching 39.6° C. (103.5° F.) the third day. By the eighth or tenth day the eruption had practically subsided.

These observers used rather severe reactions; it is possible that more satisfactory results would be obtained when, with smaller doses,

less severe reactions could be used over a longer period of time, as suggested by Van Alstyne.

More recently Klingmueller has reintroduced the injection of turpentine as a method of treatment of skin diseases. Turpentine has, as it will be recalled in connection with the work of the "Fixation abscess," been used before in therapy as a subcutaneous injection. Klingmueller, however, has modified the procedure so that quite minute amounts are injected over a long period of time. By this method 20% turpentine is dissolved in olive oil and injections of about 4 drops (0.01 turpentine) are made at 3-day intervals. Karc and others have improved the method by adding a minute amount of eukupin or novocain to the oil mixture in order to prevent any discomfort to the patient.

Klingmueller found that the injections were followed by favorable effects not only in trichophyton infections, but in acne, acute dermatitis, eczema, salvarsan dermatitis and strophulus as well. In lupus vulgaris and in tuberculous glands he observed typical focal reactions. There was no evidence of kidney irritation following the injections.

A number of observers have worked with this method. Thus Holzhäuser and Werner reported excellent results in the treatment of leg ulcers and impetiginous skin conditions. Appel, too, has tried it in a series of cases. In all the staphylococcic infections (furunculosis, acne-like eruptions and pyoderma, in moist eczema, in pruritus universalis,—both essential and symptomatic—and in urticaria) Appel reports quite remarkable improvement in most cases. Lupus reacted to the injections just as it does to tuberculin. In the deeper nodules of trichophyton infection a gradual lessening of the infiltration and size of the foci was noted. Gewalt reports the treatment of pemphigus by the same method.

Löwenfeld and Paulay have made a very careful study of trichophyton infection, treating cases with three different methods, one series on a strictly specific basis with trichon, an autolytic product of the infecting organism; one series with a nonspecific protein—tuberculin; the other with a nonspecific chemical agent—turpentine, recognizing, of course, that when injecting the turpentine it represented a form of protein therapy, in this case homologous protein from the inflammatory focus produced by the turpentine. There was little or no difference in the therapeutic end result whether the specific or nonspecific methods were used. The deeper nodular infiltrations were gradually absorbed under the course of the injections, the more superficial lesions showed less improvement. Löwenfeld and Paulay suggest that this result is to be expected in that the more superficial lesions, like those of favus, microsporia, pityriasis versicolor, erythrasma, etc., are much less susceptible to the general metabolic change that is brought about either by specific or nonspecific therapy.

Fischl treated 50 cases of trichophyton infection with turpentine

injections and resorcin, using resorcin as a local application and giving turpentine injections every two days. He commenced with a dose of 0.25 c.c. of the 20% turpentine in olive oil, advanced to 0.5 c.c., then followed to 0.75 and 1 c.c. doses during the course of the treatment. He found the treatment of great value in the deep indurative forms; in these, injections of trichophytin were also found useful. The cases were cured as a rule in about 3 weeks; the fungus disappeared from the lesions generally during the course of the first week. In four cases (of 30) there was some temperature reaction after the injections, one of these cases reaching 39.6° C., but Fischl does not consider the clinical effect in any way depending on the degree of temperature rise.

Müller used turpentine diluted with paraffin oil in the treatment of trichophyton infections with satisfactory results. He used no local treatment. There was no evidence of kidney irritation following the injections. Grabisch began the use of turpentine injections in the same condition and gradually extended his use of the injections to acute eczema, dermatitis, drug eruptions, gonorrhoeal complications, urticaria, strophulus, erythema multiforme, dermatitis herpetiformis, furunculosis, pyoderma, etc.

Ruete, on the other hand, found that turpentine injections were not followed by particularly favorable results in trichophyton infection although he obtained very satisfactory results in furunculosis. Schmidt (H. E.) reached the same conclusion. Using Klingmueller's method he treated 8 superficial cases and 6 with deep seated lesions. In the latter cases the results were far better than in the superficial ones, but even these were not cured. In 5 cases of furunculosis his results were very satisfactory. Schedler's results were more satisfactory.

Sachs recommends intravenous injections of hexamethylenamin (40% sol.) in the treatment of deep trichophyton infection, with large nodules. As a first dose 6 gm. (15 cm. of fluid) are injected; on the second or third day after the first injection the dose is increased to 8 gm. In one case 8 gm. were given as a first dose, which was increased to 12 and 14 gm. The number of injections required and the exact quantities of hexamethylenamin that will be needed cannot be definitely stated in advance. Of ten patients so treated, one was cured after a single injection of 4 gm., another after three injections of 4, 6 and 8 gm., respectively, in ten days; another patient received four injections (once 6 gm. and three times 8 gm.), and was cured in fourteen days.

Singermann found turpentine injections (10%) useful in furunculosis and in eczema, and Becker reports success in the treatment of various dermatoses.

Reese used milk injections (aolan) in 175 cases of trichophyton infection. He found that the cases were as a rule cured in about three

weeks, the number of injections averaging about 3. Scholz and Kraus and Müller also report favorable results from milk and aolan injections. Loeb used "leukogen," a staphylococcus vaccine of which large doses are injected, with success. Antoni found "aolan" satisfactory in trichophyton infection. Sellei, in comparing the value of milk and turpentine injections, found that the milk effect was more sustained and continuous. He obtained very satisfactory results in universal pruritus, and in superficial skin suppurations; in the deeper lesions the effect was less apparent. In eczema he obtained no results.

The work of Engmann and McGarry, of Scully and of Van Alstyne in the treatment of psoriasis has already been mentioned. Cemach has used tuberculomucin in one case with favorable results, while Konteschweller calls attention to the fact that all colloidal injections, just as vaccines and heterovaccines, act on the general system of the patient and improve his physical condition and in so far are useful in the treatment of psoriasis. It is just this fact that Sabouraud emphasizes. He considers that the treatment of psoriasis has entered on a new era of late with the discovery that certain measures which have nothing in common, except that they all give a kind of shake-up to the organism, are proving effectual in certain cases, although not in all. The list includes injection of mercurial salts, of antitoxic serums, and of emulsions of killed microbes from the patient's stools. He hopes that still more effectual means of inducing the shake-up or shock may yet be found. The field of experimentation seems immense and almost unlimited. Sabouraud finds Danysz' enterovaccine from the stools to be harmless, and great improvement under it seems to occur in more cases and to last longer than with any other measures yet known.

In five cases that Cadbury treated with typhoid vaccine excellent temporary results were obtained but they all relapsed sooner or later.

Just as furunculosis has been very satisfactorily treated with vaccines of all kinds, so other and less specific methods of treatment have been followed by considerable clinical success. Kaiser claims results following the injection of "tebelon" (the isobutyl ester of oleic acid), Schedler used turpentine injections, Morris and Levinson colloidal metals, and milk injections have also found extensive employment.

The eczemas, both the dry and exudative types, have been more or less resistant to nonspecific therapy. Spurgin tried salt infusion without apparent effects, while Cadbury treated 4 cases with typhoid vaccine and observed practically no improvement.

A number of other skin lesions have given more promise of success. Schrameck reports a case of pemphigus treated successfully; Cadbury treated two cases of lichen planus with typhoid vaccine which improved and one case of erythema nodosum which was cured after two injections. Hebermann was successful in the treatment of hys-

teric dermatoses. In lichen rubra Spitzer found that he obtained successful therapeutic effects with salvarsan injections provided that a typical Herxheimer reaction followed the injection, i.e., the salvarsan acted as a nonspecific agent in bringing about plasmaactivation.

Ziembowski is so far the only one who has reported cases of actinomycosis treated with nonspecific injections. He used milk in three cases with excellent results.

Kingsbury and Bechet have but recently called attention to the favorable influence of blood-letting on certain dermatoses. Venipuncture, according to the researches of Luithlen, represents a nonspecific method closely allied to the other and more mild methods of treatment which have their chief effect in alterations in the permeability of the capillaries. Achard and Flandin make use of the same phenomenon. They state that in conditions in which the factor of anaphylaxis is evident, the serum acquires what they call cryptotoxic properties, and can be utilized to desensitize. They give it in minute doses below the level of those inducing shock or even the hemoclastic crisis, injecting subcutaneously 0.5 c.c. of the autoserum; twelve hours later, 1 c.c. and the next day 1 or 2 c.c.; 2 c.c. the following day, and then every second or third day. Recurring urticaria, angioneurotic edema and hay-fever yielded promptly to this treatment, but little effect was apparent in asthma. Their experience with hay-fever has been limited, but one case cured in 1918 had only very slight symptoms the following year. The effect of this treatment is not like that of ordinary serotherapy but seems to be an actual desensitization.

## CHAPTER XVI

### DISEASES OF THE EYE

Isolated instances of successful vaccinothrapy when large doses of organisms were employed in certain cases of eye diseases have been reported during the past ten years or more, as for instance by Grey, Gorbunow, Bryan and by Allen. Römer treated hypopyon keratitis with large doses of vaccine and also used autoserotherapy with some success, using the patients' serum drawn from a blister. A large number of other observers, Darier, W. Zimmermann, Fromaget among them, successfully used diphtheria antitoxin injections. v. Szily used huge doses of gonococcus vaccine (arthogon) in the abortive treatment of ophthalmoblennorrhoea with surprisingly good results, but it was not until the report of Müller and Thanner was published that much attention was given to therapy of this nature. In fact, the use of nonspecific therapy in the treatment of eye diseases may be stated to date from their observations.

Müller and Thanner injected 5 c.c. of milk intramuscularly in 4 cases of parenchymatous keratitis, all of whom improved, as did likewise 11 cases of iritis. It was noted that when the iritis was due to gonococcus infection the improvement was not as prompt as in those of rheumatic origin or iritides of undetermined etiology. In these the pain and photophobia disappeared in 24 hours. In nine cases of corneal opacity (without choroiditis) little improvement was observed, nor did they see any effect on choroiditis.

Friedländer began the treatment of trachoma, using a somewhat larger dosage (10 c.c. of milk intramuscularly injected). In 42 cases so treated the results were reported to be excellent. Injections were given every 4 days.

Hühn had noted previously that trachoma cases under his care in a hospital for children improved remarkably during the course of a scarlet fever epidemic and then tried out the use of milk injections, too, in order to simulate the clinical picture of the spontaneous disease. He reports that with the milk he obtained excellent results. Rosenstein treated trachoma with milk injections with satisfactory results; Königstein, in a discussion at the Gesellschaft für Aerzte at Vienna, stated that in some thirty cases he had witnessed both increased irritation and also improvement in his cases. Blatt does not believe that the method is useful. Pflugk, also using milk, obtained good results in iritis, in keratitis parenchymatosa and in adult blennorrhoea.

Heinemann and Wilke report excellent results with milk injections in adult blennorrhœa and severe eye infections.

Three rather extensive reports have recently been published, those of Possek, of Berneaud and of Jendralski. Possek (as well as Haab) used a typhoid vaccine, killed with phenol and made up with approximately 500 million organisms to the cubic centimeter. Of this he injected from 0.6 to 1 c.c. subcutaneously the first day and 1 c.c. the second day. Following these injections there was usually a temperature reaction of mild degree.

This vaccine therapy was applied to a series of eye conditions of undoubted luetic origin, 52 of which were of long standing, 32 of which were recent. Of the old cases 16 were congenital lues, the balance acquired. These cases had had mercury and salvarsan treatment for a long time before they were treated with vaccine, but without apparent benefit. Possek selected the cases that had not responded to the specific therapy for his experiments with vaccines. In a few cases where no luetic basis was at first suspected and non-specific treatment given without previous specific therapy, excellent results were obtained, although later the luetic nature of the trouble was established serologically. Among these cases, 4 of hereditary keratitis were markedly benefited, the inflammation of the iris receded and the cornea cleared up. In several cases of retinal hemorrhage the hemorrhage was resorbed, and in cases of turbidity of the lens, a definite clearing was observed. Good results were obtained, too, with optic neuritis.

A large series of cases (500) have been reported by Berneaud. Berneaud gave over 2,000 injections of milk to these patients and his results are of considerable interest. He obtained little or no result in the treatment of glaucoma, amotio retinae, lacrymal duct inflammation, neuritis, neuroretinitis, multiple sclerosis, in keratitis parenchymatosa or ophthalmoblennorrhœa.

On the other hand, in keratitis eczematosa and scrofulosa, and in secondary glaucoma following iritis marked improvement was noted. In 70 cases of iritis 60 were cured or markedly improved after the injection. In 24 cases of choroiditis 6 were much improved, 10 partly improved and 8 not altered. In his trachoma cases he found that the corneal ulceration was improved while the connective tissue inflammation of the conjunctiva was not much influenced. Of 11 cases of gonorrhœal conjunctivitis 9 responded very well. On a concomitant vulvovaginitis in some of these cases there was no apparent effect. Herpes of the cornea was also favorably influenced.

Jendralski treated 100 cases of eye disease with milk injections. In phlyctenular disease some improvement was observed, more often in the subjective direction than in objective alteration. Trachoma was not altered and in corneal ulceration Jendralski urges great caution lest actual perforation may follow. In iritis the results were excellent;

several cases of ophthalmoblennorrhoea improved rapidly. In tuberculous iridocyclitis the improvement was not marked.

Both Igersheimer and Kraupa obtained remarkable results in iritis and found that in gonorrhoeal disease the results were usually very satisfactory both in adults and in children.

Jacovides treated about 221 cases of ocular disease with nonspecific therapy. In 150 cases of ulcer of the cornea 140 were cured after 2 to 3 injections.

Jickeli, using milk, treated ophthalmoblennorrhoea, iritis, choroiditis and ulcers of the cornea with satisfactory results; milk therapy has found many partisans among French and Latin clinicians, and the reports of Carreras, Darier, Dimmer, Müller, Domec, Mansilla, Argañaraz, Gaupillat, Guibert are available, while Titus and Nolf have used intravenous injections of peptone. Nolf has paid particular attention to this form of therapy in ocular complications following typhus, typhoid and septicemia. Guibert obtained his most satisfactory results in scrofulous diseases. Gaupillat obtained very satisfactory results in hypopyon keratitis and in bulbous infection. He used milk injections for subconjunctival injection in one case.

Darier, one of the earliest advocates of paraspecific therapy, used milk injections together with oral administration of serum, which, as Cumston has recently mentioned, is so frequently used as a routine by French clinicians. Darier's results in infectious ulcers of the cornea and in iritis—traumatic as well as postoperative—were very satisfactory. In keratitis parenchymatosa and in trachoma he does not consider his results conclusive.

Darier has been indefatigable in his advocacy of the oral administration of serum, claiming that with little reaction on the part of the patient the polyvalent serum exerts a systemic stimulation comparable to the effect of milk, peptone or colloidal metals injected into the patient. According to Darier some diseases are affected more by one than the other of these agents so that some clinical experience must be gained before it is possible to use them with greatest success.

Quite a number of observers have reported on the use of milk injections in the treatment of ophthalmoblennorrhoea, among them Jickeli, Nassbaum, v. Liebermann, Purtcher, Müller, Holler, Sommer, Hönig and Bachsteg, all but the latter noting marked benefit following the milk injections. Liebermann undertook the treatment of a large series of cases of gonorrhoeal ophthalmia in adults with milk injections, but at the same time did not fail to continue the usual local treatment. He found that the effect of the injections on the symptoms was as follows:—The secretion usually ceased after the first or the second injection and only rarely recommenced. The demonstration of the organism in the exudate became more and more difficult as the effect on the amount of secretion became apparent; only in exceptional cases did he obtain a positive bacterial finding after the secretion had

diminished. The primary effect of the injections was a chemosis after which the evidences of inflammation rapidly diminished. Ulcers of the cornea were prevented; if already present they were arrested; Liebermann observed only one corneal perforation in his entire series of about 100 cases. Liebermann made use of injections of a manganese colloid with excellent results.

The most extensive treatise on the subject has been published by Uddgren at Stockholm, while other Scandinavian oculists have reported conflicting results—Lundsgaard, Andersen, etc. Uddgren used milk injections (sterile milk, boiled, with very little reaction on the part of the patient) in about 100 cases of eye diseases. The results were as follows:—

*Conjunctivitis aestivalis.* Three cases. Prompt recovery.

*Trachoma.* Three cases. Improved.

*Conjunctivitis phlyctenulosa.* Fifteen cases. All improved, subjectively as well as objectively.

*Keratitis parenchymatosa.* Fifteen cases. Of these twelve positively luetic, the others probably tuberculous. Results inconclusive.

*Keratitis profunda.* Five cases. Four cured; the fifth case had a relapse after three months—panophthalmitis.

*Maculae cornea.* Twenty-four cases. Improved vision in some cases; in a few of these the result was not permanent.

*Scleritis and Sclerokeratitis.* Seven cases. Without specific therapy the milk injections result in only transient improvement. Combined with specific therapy Uddgren obtained good results.

*Iritis and Iridocyclitis.* Eight acute cases. Cured or much improved. Four subacute. Improved. Four chronic plastic type. Improved.

*Opacitates corp. vitr.* Eleven cases. Stimulating and resorbing effect of the injections marked in some cases.

*Ablatio retinae.* Three cases. No permanent improvement.

*Ocular nerve lesions.* Neuritis improved and in some cases complete cure. Atrophy of nerve not improved in single case injected.

*Paresis N. abducent.* Two cases. Recovery accelerated.

Chevallier has used collargol intravenously in cases of septic iritis and in keratitis with good results, while Boyd has reported good results by using typhoid vaccine intravenously in cases of iritis. Zimmermann (Chas.) has reported two cases of corneal infiltrations which improved after milk injections.

Veach has recently contributed some experimental data concerning the value of nonspecific therapy in ocular infections due to idiopathic origin. Reber has in his classification observed that iritis is usually due to one of 5 organisms—the spirochete, the tubercle bacillus, the gonococcus, the pneumococcus and the influenza bacillus. The spirochete is responsible for some 30 to 60% of these. Assuming that we have sufficiently satisfactory therapy for all these specific infections, there still remain a large number in which our therapy is

seemingly ineffectual, cases of indefinite etiology—rheumatic, metabolic, etc. It is for this group that Veach considered nonspecific therapy of utmost usefulness.

Veach produced experimental iritis by injecting streptococci, both viridans and hemolyticus, and staphylococcus aureus into the iris of rabbits. These were then treated with intramuscular milk injections. The course of the disease in the treated rabbits was definitely shortened as compared to rabbits similarly infected but not treated with milk. Veach considers the experimental results sufficiently encouraging to warrant the use of this nonspecific method of therapy in clinical practice in all cases of iritis of uncertain origin.

Stocker, instead of injecting milk intramuscularly in eye cases, has used it intraperitoneally. The method as used by him consists of injecting from 3 to 12 gm. of cow's milk (boiled for three or four minutes) into the peritoneal cavity. A fever that persists for from two to three days results. His results in eye cases have been very good.

Musy pasteurizes milk for 15 minutes and injects 5 c.c. intraglutely every 2 to 4 days. He was amazed to observe the rapidity with which the pain, injection, photophobia and the swelling diminish under the course of such injections.

In iridocyclitic processes the results were excellent; in iritis the pain subsided, the pupil dilated and corneal defects showed early vascularization; even in luetic cases with the formation of synechiæ, the milk injection assisted the systemic specific treatment.

On the other hand, with chronic iridochoriocyclitis, in blennorrhæa neonatorum and in tuberculous iridocyclitis the treatment seemed to have little effect on the course of the disease.

Klingmueller reported that with turpentine injections five cases of ophthalmoblennorrhæa cleared up very promptly.

Peltesohn has studied in particular scrofulous diseases of the eye and their treatment by nonspecific means and by the Ponndorf method of intracutaneous tuberculin treatment. He found that the severe and moderately severe cases responded well to the latter method while almost hopeless cases were very favorably influenced by suitable combined treatment with the casein and the tuberculin injections.

The report of Heine must finally be mentioned. Heine reports the results of his experiments with subcutaneous injections of milk in albuminuric retinitis. The dosage was from 5 to 10 c.c. If we regard the checking of the deterioration of vision as due in all cases to the milk injections, then out of 17 eyes, 15 were favorably affected thereby. If we consider only such cases as being favorably affected in which there was a marked improvement of vision, the favorable results numbered 11, whereas in 4 the disease process was only stayed. In only 2 did the disease process continue in spite of the injections.

Also a series of cases of infectious retinitis and choroiditis was treated with milk injections. The primary results were often excellent, though recurrences were common. Schwarte treated a series of severe infectious processes with milk injections and reports that the results were very apparent, most of the cases being favorably influenced.

## CHAPTER XVII

### INFLAMMATION

The studies that have been made in recent years which deal with the healing of wounds and the factors that favor or retard bacterial growth in wounds have added much to our understanding of the fundamentals of local infection and resistance.

We must keep in mind the following facts. Injured tissue—contused—burned—fragmented or altered to such a degree that its circulation is markedly interfered with is a twofold source of intoxication. As it becomes necrotic—even though sterile—it produces protein split products which are profoundly toxic to the organism and cause either a febrile reaction if relatively small in amount, or complete prostration and shock if larger in amount. Very likely the mere liberation of tissue (cell) juices without digestion can bring about similar effects; in animal experimentation the toxicity of the tissue extracts is, of course, well known, where their effect on the coagulation mechanism usually brings about an acute shock picture and death. Nägeli has emphasized the importance of tissue necrosis, even when aseptic, in general pathological problems. Experimentally it has been found that the products of tissue contusion can kill an animal and the investigations on the production of shock made during the recent war by a number of American investigators have also served to focus our attention on this practical problem. Nägeli, among other experiments, took small pieces of tissue, permitted them to autolyze for 24 hours aseptically and found that on reimplantation the animal died as a result of the absorption of the toxic split products from the autolyzing material. Even sterile blood (autogenous) will, when free in the tissues, cause a considerable leukocytosis (Dold), and Freund has recently published interesting studies that demonstrate the formation of toxic substances from blood. Secondly, the altered tissue permits the establishment of bacterial invasion against which normal tissues would be amply able to protect themselves.

For the first twelve or twenty-four hours following injury (the so-called preinflammatory stage) infecting organisms are confined to the surface of such wounds. If during this period the injured tissue is excised (debridement) we remove the potential sources of intoxication as well as the opportunity for infection, and healing by primary intention is the rule.

When once this pre-inflammatory stage has been passed and bac-

teria have found lodgment and have become established, then we have to deal with the invasive power of the organisms on the one hand and the factors of resistance of the body on the other. To Wright we are considerably indebted for his contributions to this particular field and Flemming has discussed the subject in a comprehensive manner in a recent paper.

According to his view the rôle of antiseptics in the treatment of wound infection is problematic. Flemming believes that all solutions that are at all effective have no appreciable bactericidal titer in the wound, but that they act as mild tissue irritants leading to increased leukocytic emigration and to more abundant flooding of the wound with normal tissue fluids, in this way hastening the separation of sloughs and the elimination of bacteria. He regards the antiseptic method of Dakin and Carrel, for instance, as fundamentally dependent on the same principles as that of the so-called physiologic method of Wright.

It is quite apparent from his study that both the leukocytes as well as the enzyme-antienzyme content of the blood serum and tissue fluids have considerable bearing on the healing of wounds.

Application of these principles was made by Wright in the use of hypertonic salt solutions (clinically not successful to the degree anticipated, because of the discomfort to the patient); the use of concentrated sugar solutions; and the use of nonpathogenic bacteria which, when introduced into the wound, seemed to have a favorable effect on inflammation. The so-called "Reading" bacillus seems to have been one of the most successful of the bacteria of this type. This was a spore bearing anaërobe of saprophytic nature, to which the name "Reading Bacillus" was given by Donaldson. He describes it as follows:

"It is highly resistant to heat and drying, and grows best in a slightly alkaline medium. It most closely resembles *B. sporogenes* (Metchnikoff). It is nonpathogenic for animals as well as for man when introduced into septic wounds. It does not attack living tissues. The use of salt is not necessary for the successful treatment of gunshot wounds, as was thought by those who advocated the salt-bag method. The success depends rather on the activity of this particular bacillus under conditions favorable to its growth and not on the salt. The rationale of the method depends not on inhibition by the Reading bacillus of the growth of pathogenic organisms in the wound either by reason of the formation by the bacillus of an inhibitory organic acid, or by the production of any bacteriolytic ferment. It acts, however, by virtue of its proteoclastic enzymes as an organic catalyst which hydrolyzes the substrate of dead protein. It disintegrates the protein base from which pathogenic organisms operate, and while so doing does not itself give rise to fresh toxic substances. Not only so, but it is probably able to hydrolyze also the

toxic degradation products of other organisms. In support of this theory, a résumé is given of experiments on tetanus and other toxins, which show that the Reading bacillus, out of a series of organisms investigated, is alone able to reduce the toxicity of these toxins. There is one exception, namely, *B. sporogenes* (Metchnikoff), which, however, does not appear to be so potent in this direction as is the Reading bacillus." Donaldson suggests that this ability to modify a toxin like that of tetanus may prove to be of value as a means of differentiating various types of proteolytic organisms, while it introduces new ideas in regard to the biologic processes going on in septic gunshot wounds.

In the discussion of the effect of nonspecific injections on the bubo, the influence of the enzyme and antienzyme changes have been fully discussed in their bearing on local inflammatory processes, so that it will not be necessary to repeat the conception of the mechanism involved. It should be kept in mind, however, that the effect of nonspecific injections is a diphasic one: we deal at first with a peripheral leukopenia, a lowering of the antiferment titer, an increase in the protease, an increase in the permeability of the capillaries, in the irritability of the nervous system, most probably an increase in the susceptibility to intoxication. This is the negative phase which makes its effect apparent on local inflammatory changes by an increase in the symptomatology. This phase is followed by a positive one in which the reverse of all these biological alterations takes place, and usually to a degree measured by the intensity of the preceding negative phase. On the basis of this mechanism we can determine to a certain degree what we may expect from nonspecific therapy and what its limitations will be. If, for instance, we have existing a large inflammatory focus with much absorption of necrotic material, with a marked leukocytic reaction and a high temperature, nonspecific therapy will be absolutely without effect in the majority of cases because the absorption from the inflammatory focus is already doing the same thing that we would attempt artificially. In a phlegmon the treatment is surgical, not expectant or nonspecific. On the other hand, in a lymphangitis or a lymphadenitis, as Kaiser has shown, excellent results may follow nonspecific injections just as they do in the case of the bubo.

Despite the fact that Gellhaus has reported favorable results in the treatment of appendicitis by means of collargol injections (in 34 cases only 6 were operated) the fact that the nonspecific injection is first followed by a negative phase with intensification of the disease process would, in my judgment, definitely exclude all such and similar acute surgical conditions from the field of its application.

Gellhaus has reported on a very extended series of cellular inflammations (143 cases) treated with intravenous injections of small doses of collargol and seems very much impressed with the possibilities.

In 31 cases of cellulitis 17 healed without surgical interference. Schubert, on the other hand, tried turpentine injections in 80 surgical cases of all kinds, but his results were not satisfactory; Wederhake and Chiaudano have also given the method a trial, the latter with success in mastitis.

On old chronic inflammation and sluggish ulcers much more can be expected and a number of favorable reports have been published. Gow, for instance, treated an old sluggish ulcer with intravenous injection of streptococci, using a dosage of 100 million, with good results. In this case the reaction was delayed considerably as compared to the reaction that follows typhoid or colon injection. The pulse rate showed some change after 4 hours but the febrile rise did not begin until about 10 hours after the injection. There was some nausea and a headache which began twelve hours after the injection and persisted for 36 hours. There was practically no leukocytic response.

Zalewski and Müller have also reported on the treatment of old ulcers and more recent wounds with milk injections (aolan) and obtained very satisfactory results.

Heterovaccination has found many adherents among French clinicians, and in a recent discussion of the Société de Chirurgie at Paris the treatment (especially by the method of Pierre Delbet), particularly of carbuncles and similar surgical conditions, was taken up. Pierre Delbet combines the Pasteur method of attenuated cultures with the modern method of killed cultures. He found it possible by this means to inject a considerably larger dose, several billions of microorganisms, at one time. Despite the massive dose, he has never observed any reaction analogous to that described by Wright as the negative phase, which Delbet thinks is the result of an excessive initial dose. On the contrary, certain toxic reactions were observed, often very violent, and despite their intensity, these were found to constitute a good omen. In the process of aging, the toxicity of the culture is probably attenuated though not entirely destroyed. After some attempts, Delbet fixed on 4 c.c., representing about thirteen billions of organisms, as a safe and effective dose. The vaccine is, naturally, a stock vaccine of streptococcus, staphylococcus and *Bacillus pyocyaneus* (the last in great abundance: eight billions). Delbet believes it unnecessary to use the specific micoorganism and, like Wright, he has not only abandoned autogenous vaccines, but he even questions whether better results are not obtained with a vaccine prepared from cultures of a micoorganism other than that which is the causative agent in a given case. The method has been employed since 1913, since which time no case of carbuncle in Delbet's service has been treated by surgical incision; boils, lymphangitis and erysipelas also respond very promptly to this treatment.

Renaud has used typhoid vaccines in the treatment of phlegmons,

while Höfer found that he at times obtained very satisfactory results from milk injections in carbuncles and phlegmons.

A related procedure is that of the production of a nonspecific reaction before some surgical procedure in order to make the patient more resistant to infection and a considerable literature of rather inconclusive nature has been accumulated. Nucleins were the favorite agents, injections being made usually from 36 to 48 hours previous to laparotomies in order to prevent peritonitis. De Paoli and Calisti, for instance, report on two hundred cases in which such injections were made and an increased resistance against infection claimed. Experimentally they determined that apart from the leukocytosis produced by such injections, bactericidal substances for colon bacilli could be demonstrated in increased amounts after the injections.

Stracker used milk injections with the idea of increasing the general resistance of patients before operation and utilized reamputation cases for the purpose. He had observed that in old infected stumps subjected to reamputation, infection of the new area was almost a constant result because of the poor condition of the patient generally and because of the lowered local resistance of the tissues. To increase the resistance he injected 10 c.c. of sterile milk three times before the operation, at two-day intervals. In fully half of the cases he observed a focal reaction at the site of the old lesion. His results were as follows:—In 43 cases of reamputation without preceding milk injections 10% healed by primary intention; in 72 cases with preceding milk injection 49% healed by primary intention. In 37% of the former cases there was suppuration, while in the "milk" series only 13% suppurated.

Closely related to these observations is the observation made by Stuhl, that infected wounds heal more rapidly after typhoid inoculations. Perhaps the recent paper of Bier's as well as the discussion which followed its presentation at the Berlin Medical Society will be found of particular interest because it covers in a broad way the entire subject of inflammation and our present methods of therapy, with specific, nonspecific and physical means.

## CHAPTER XVIII

### INDICATIONS AND CONTRA-INDICATIONS

Protein therapy offers a potent, perhaps the most potent, method that we have at our command of altering the current of cellular activity in two diametrically opposite directions—acceleration of function and depression of function. If the agent that we inject is very toxic and the dose large, acceleration soon gives place to fatigue, to complete exhaustion and finally to death; if relatively large doses are repeatedly given the condition of protein cachexia, observed in experimental animals, might supervene. Proper dosage, on the other hand, results in transient but well marked stimulation without clinically apparent fatigue, and if continued for a period of time the alteration of acceleration and depression of metabolic processes becomes clinically manifest in increased weight and general well being.

It is apparent how far-reaching the field of application must be and how difficult to make definite rules of procedure or to advocate certain methods or preparations. The extent of usefulness of a method that is a true "plasmaactivation" in the strict sense of the term forbids a definite delimitation to narrow confines. But despite theoretical possibilities, actual practice might perhaps reduce the clinical application to very modest dimensions. In this connection I would quote the opinion of Schmidt, who believes that we shall some day come to regard a course of protein therapy in the same light that we now do a change in diet, a change in climate, a course of baths; that is, apart from its usefulness in acute diseases, we shall accept protein therapy in its various modifications as one of the very first and the most commonplace of methods of therapy.

With these considerations in mind we can intelligently apply protein therapy in infectious diseases only if we fix very firmly the concept that nonspecific therapy is purely a method of stimulation whereby all the forces of cellular and humoral resistance are for a short period of time keyed to the very highest pitch and by reason thereof, stimulation of this character is useless when the cells of the body are profoundly fatigued.

As with other new therapeutic procedures there is still some uncertainty as to the proper dosage. Especially is this true because the dosage depends to some extent on the vigor of the patient, on the type of infection which is causing the disease, as well as on the stage of the disease. There is no unanimity of opinion whether it

is well to give one or two fairly large injections or several smaller ones. Whatever method is used it is well to be cautious, especially when dealing with such toxic substances as vaccines.

Before applying the treatment to any acute disease it would seem that prudence would demand a thorough familiarity with the range of the reaction and the degree of toxicity of the preparation it is intended to us, by first employing it in some arthritic cases. In arthritis, when we exclude alcoholics and old cardiac cases, the dangers of untoward effects from the reaction are minimal and with reasonable caution nonspecific therapy is not only without risk but indeed frequently followed by gratifying clinical improvement. Only in the light of experience so gained would it seem permissible for us to attempt to extend this form of therapy to other acute infections.

In general it is to be kept in mind that injections must be given early in the course of the disease; that the injections should be given slowly; that relatively small doses should be given the first time and that care must be taken, if intramuscular injections are made, that the injection is not by accident intravenous.

For intravenous injections the protein split products are, for obvious reasons, more satisfactory than vaccines; if a relatively mild reaction is desired the various serums are very useful. Where a moderate reaction (general and focal) is desired, intramuscular injections of boiled market milk are to be considered; if less general but some focal effect is desired, Uddgren believes that milk with a low bacterial count (certified milk) is to be preferred.

The possibility of a certain degree of selective action of some of the agents is not to be ignored, the use of staphylococcus and pyocyanus vaccine mixtures in the treatment of neuritis being such a case. In hemorrhagic disease the use of serums and of milk or salt solutions is to be preferred to vaccine or proteose injections, because of more marked effects in hemostasis.

It should not be necessary to point out that the nonspecific method of treatment should under no circumstances be considered as a rival or a substitute for the proven specific measures that we have at our command. That a nonspecific factor is at times and possibly often associated with the specific reaction may be true, the more reason that both should be studied and both utilized in their proper time and place. From the evidence so far gathered, the use of the specific measures is always in place whenever a true toxin is to be neutralized by an antitoxin; on the other hand, the nonspecific measures find a field of usefulness as adjuvants of drug therapy in the treatment of syphilis, both early and late, with quinin in malaria, with salicylates in arthritis, with luminal in epilepsy, etc. Here the injections serve at least two purposes. They facilitate the diffusion and distribution of the drug and they increase the general resistance of the patient.

Apart from the early use of the nonspecific agents in the hemorrhagic diseases, their use in methods of desensitization, not only in cases of asthma where we can find no specific cause, but in angioneurotic edema, urticaria and certain of the gastro-intestinal conditions to which Danysz has given particular attention, is one of considerable importance.

Finally we have to keep before use the therapeutic application of these agents in the focal reaction, where both the sharp effect of intravenous vaccine injections (as in iritis) and the milder effect of repeated injections of turpentine have found definite spheres of usefulness.

### CONTRA-INDICATIONS

The effort has been made throughout this treatise to make it clear that the nonspecific reaction is a diphasic reaction, the first effect being the intensification of the disease manifestation both generally and locally, the second being a constructive phase in which there occurs a general euphoria, a diminution of disease symptoms both generally and locally, with at times complete restitution to the normal. Generally speaking it has been found that the more severe the first phase the greater the clinical benefit. This augmentation of the disease symptoms must be kept firmly in mind. No patient should be subjected to an intravenous injection normally followed by a severe reaction (typhoid or colon bacilli, protein split products, etc.) unless there is every evidence that the patient is a good clinical risk and able to bear the additional strain imposed by the injection. If nonspecific therapy is desirable in the more uncertain cases some of the less severe methods can be employed with much less danger, such as intramuscular injections of milk, nucleins, turpentine, etc. Another and equally important deduction can be drawn from the recognition that the reaction is a diphasic one that depends on stimulating the cells. Therapeutic results cannot be expected when the organism is no longer capable of response to stimulation. When complete fatigue has been reached no amount of stimulation will avail and the additional burden imposed by the material injected can only harm the patient.

One observes not infrequently in the American literature the use of relatively large doses of such agents as typhoid vaccine, colon vaccine and similarly toxic substances. It would appear to be not only necessary but quite irresponsible to subject patients to such severe methods. One can usually obtain a very satisfactory reaction with moderate dosage and this without unusual risk or inconvenience to the patient.

Particular care must be observed to obtain a history of hypersensitiveness on the part of the patient—serum sickness—asthma—urticaria—angioneurotic edema—or of epilepsy or other grave nervous instability. In such cases the more active agents must not be used.

Alcoholism, of the type that one encounters not infrequently in charity hospitals, is an absolute contra-indication. We have records of several patients who developed delirium tremens after nonspecific injections, one ending fatally.

Pregnancy must be similarly regarded as an absolute contra-indication.

In the various cardiac lesions great caution must be observed. We would include not only severe valvular injuries but cases with high blood pressure, with arteriosclerosis, myocarditis, or with evidences of vasomotor instability. In typhoid we have found it a good rule to exclude all cases with a pulse rate over 100; indeed, every case of acute infectious disease should be carefully gone over for evidence of myocardial impairment before injections are made. In well compensated valvular lesions we have injected typhoid vaccine with relatively severe general reactions without ill effects. The left heart border may be observed to extend outward for a centimeter or so, but as a rule there are no evidences of decompensation. v. Groer has fortified patients that were not in exceptionally good vascular tone by giving small doses of digitalis for about two days before injections were made.

Diabetes is considered a contra-indication by Lindig who was of the impression that because of the vascular changes often associated with the diabetic condition the diabetic should be excluded. Uddgren also excludes the diabetic.

In typhoid we have excluded the older cases (third week) from treatment, as well as cases that were septic or had evidence of septic or pulmonary complications. Naturally any evidence of bleeding either from the nose, stomach or bowel would exclude nonspecific therapy. The earlier workers observed several deaths from epistaxis following intravenous typhoid injections when these precautions were not observed.

Neither old age nor infancy is considered a contra-indication by Uddgren.

The patient does not become sensitive to the injection of heterovaccines or of proteoses; on the contrary, with succeeding doses there is increased tolerance until several multiples of the original dose must be injected to elicit the proper reaction. Sensitization to serum is not only possible but occurs not infrequently, usually not to any degree that need cause alarm. Smith has made use of this increased sensitization to serum to obtain shock reactions and therapeutic results therefrom. With milk the conditions are somewhat different. Some observers, including Bessau, Decastello and Mueller, consider the milk injection and its effect as due practically to the bacterial content, i.e., a heterobacteriotherapy. Considering the popularity of the milk injections in Europe, there have been relatively few reports

of sensitization from it, or severe collapse following after repeated doses. It has been suggested that this is due to the fact that the milk is boiled and so dedifferentiated. Hecht made intracutaneous injections of milk in patients injected previously with milk and also in noninjected patients. There was no difference in the skin response, nor was he able to demonstrate milk antibodies.

When heterobacteriotherapy was first introduced and the dosage and the results were very uncertain, deaths incident to the injections, such as were reported by Eggerth, Kraus and Mazza, Boral, v. Reuss and others, were perhaps excusable. Large doses of typhoid vaccines were used because of the impression that such amounts were essential to elicit the reaction. With further experience such disasters have been eliminated and less violent methods have come into use whenever the patient is not in good condition. Untoward results can no longer be attributed to a fault in the method of therapy but to the judgment of the physician.

Needless to say, nonspecific therapy does require judgment, careful attention and bedside study on the part of the physician, perhaps in greater measure than any other therapeutic procedure. It should never be a routine; to be useful it must be an individualized therapy, with dosage and preparation and time of application varied to the disease, its intensity, its duration and the resistance of the patient. So used, nonspecific therapy should prove to be one of our most useful measures both in acute infectious diseases and chronic inflammatory lesions.

## APPENDIX

### THE PROTEINS AND THEIR SPLIT PRODUCTS

The nonspecific reaction, as we have seen, is elicited most frequently by colloidal substances, either injected therapeutically or originating in the tissues as a result of some inflammation (turpentine injection, burn, trauma, etc.). Luithlen has as a result used the term "Colloidal Therapy" to designate the form of treatment. Of the various colloids we find the proteins and their derived products most commonly used and it may be proper, therefore, to review very briefly the salient facts concerning their classification, structure and behavior.

The native proteins consist of exceedingly complex molecules which in turn are built up of combinations of amino acids. The final molecule is a large one, does not diffuse through parchment, collodion or animal membrane, frequently gives a faint opalescence in solution, is usually amorphous but when in pure form can be crystallized under certain conditions. Chemically the proteins are relatively stable and inert and are amphoteric, combining with both the hydrogen and the hydroxyl ion. They can be hydrolyzed both by acids and alkalies as well as by enzymes, yielding a series of degradation products commonly referred to as protein split products. These latter vary in character, in amount, and in composition with the protein undergoing lysis, the method used in bringing about the disintegration, and the time at which the material is examined.

For convenience we may use the so-called American classification of the proteins which divides them into three main classes:

- A. Simple proteins.
- B. Conjugate proteins.
- C. Derived proteins.

**The Simple (or Native) Proteins.**—These are naturally occurring proteins which on hydrolysis yield only  $\alpha$ -amino acids or their derivatives.

*Albumins.*—Simple proteins, coagulable by heat, soluble in water and dilute salt solutions. Ovalbumin, serum albumin belong to this group. On injection they are followed by little or no reaction unless the organism has been previously sensitized.

*Globulins.*—Simple proteins, heat coagulable, insoluble in water but soluble in dilute solutions of salts of strong bases or acids. Serum globulin is an example.

*Glutelins*.—Simple proteins, heat coagulable, insoluble in water or dilute salt solutions, but soluble in very dilute acids or alkalis.

*Prolamins*.—Simple proteins, insoluble in water but soluble in 80% alcohol.

*Albuminoids*.—Simple proteins, insoluble in dilute acid, alkali, water or salt solution.

*Histons*.—Simple proteins, not coagulable by heat, soluble in water and dilute acids; strongly basic.

*Protamins*.—Simple proteins, basic, noncoagulable by heat, soluble in ammonia.

As far as the use of these substances in nonspecific therapy is concerned interest has centered so far almost wholly on the native proteins of the serum, including serum albumin and globulin as well as fibrinogen. If the proteins used for injection include plant proteins, other members of this group will, of course, be involved. No study has been made dealing with the relative advantage or disadvantage of various native proteins for therapeutic injections.

**The Conjugated (or Compound) Proteins.**—These are compounds of some simple protein with some nonprotein group, the latter usually acid in nature. They are subdivided as follows:

*Chromoproteins* (Hemoglobins).—These are proteins in which the nonprotein addition group is colored, as hematin in hemoglobin.

*Glycoproteins* (Glucoproteins).—The prosthetic group in this class contains a carbohydrate radical. Mucin and cartilage are examples.

*Phosphoproteins*.—Proteins derived from the cytoplasm. The addition group contains phosphoric acid. Casein belongs to this group.

*Nucleoproteins*.—Proteins of the nucleus, i.e., chromatin. Nucleic acid is here the added radical. Nuclein, nucleohiston, etc., are examples.

*Lecithoproteins*.—These have not been isolated in pure form. Together with the *Lipoproteins* their existence is probable, the former consisting of proteins to which lecithins or phospholipins have been attached, the latter of proteins in combination with one or more of the higher fatty acids. It is possible that the forms are easily dissociated and vary from loose and transient physical aggregates to relatively more stable chemical combinations. Their very lability would make them of great physiological importance in cellular processes.

The *conjugated proteins* are of considerable importance from the point of view of nonspecific reactions. On injection they are followed in general by relatively little reaction, but the organism can become sensitized to these proteins just as to simple proteins of the first group. When the conjugated proteins are dissociated from their nonprotein radicals they produce a far greater reaction than when in the conjugated form. Schittenhelm and his associates have demonstrated this with the chromoproteins.

The *phosphoproteins* are of interest because casein—the isolated protein of milk—belongs in this category. This protein has been used to a great extent for the nonspecific reaction. Casein itself is followed by little or no general reaction when injected for the first time. It has been suggested that the more marked reaction obtained with milk injections is due to the bacterial content, rather than due to the protein of the milk itself. Casein is practically the only one of the native proteins which is subject to the action of erepsin, both of the enzyme of the intestinal tract and the erepsin-like enzyme occurring in the serum.

The *nucleoproteins* occur not only in the proteins obtained from nuclei of cells, but are present in large amounts in the material obtained from bacterial sources in which the nucleoprotein occurs throughout the cell body. The relation of these substances to the so-called endotoxins of bacteria is still uncertain. v. Groer isolated a nucleohiston from typhoid bacilli which he used for nonspecific injections.

**The Derived Proteins.**—This group is an artificial one and includes all the decomposition products occurring after the action of chemical, physical or biological agents (enzymes) on the naturally occurring proteins.

*In the first group* are included the proteins, metaproteins and coagulated proteins, that is, proteins which have undergone the first alterations following the action of heat, acids, etc. This group has no importance from the therapeutic standpoint.

*In the second group* are included those protein derivatives commonly called protein split products, which in turn are classified under three groups—Proteoses, Peptones and Peptids.

**THE PROTEOSES (ALBUMOSES).**—These represent the first dissociation products of the albumins. They are no longer heat coagulable but can be salted out by concentrations of certain salts such as ammonium sulphate, zinc sulphate, etc. They are by no means clearly defined chemical entities, the usual preparations obtained by precipitation including mixtures of molecules and molecular aggregates varying to some extent in size. The albumoses are roughly divided into two groups, primary and secondary albumoses. Of these the *primary proteoses* more closely approximate the proteins from which they are derived; they are precipitated by half saturation with ammonium sulphate.

*The Primary Proteoses* can in a general way be divided into two groups by means of dialysis, whereby the hetero-albumose becomes insoluble, or by the addition of an equal amount of alcohol. Hofmeister's table may be of some value in illustrating the differences in behavior of these higher split products of proteins.

In general it may be stated that the primary proteoses are more toxic than the secondary proteoses, but variations occur, depending

Hofmeister's Table

	Precipitation		Water sol.	Alc. sol.	Diffusibility	Biuret
Primary Albumoses (Proteoses)	Ppt. in from 24 to 42% Amm. Sulphate	Proto-Albumose	Readily sol.	Sol. in 80%	Good	+
		Hetero-Albumose	Not sol., but sol. in dil. salt sol.	Insol. in 32%	Poor	+
Deutero- or Secondary Albumoses (Proteoses)	54% to 62%	A. Thio-Albumose	Sol.	Insol. in 60%-70%		+
	70% to 95%	B. Albumose Syn-	Sol.	Vary		+
	100% + Acid	C. C-Albumose	Sol.	Sol. in 67%-80%		+

no doubt on the chemical composition of the original protein from which the split products are derived. Kaznelson has reported observations in this connection with protein split products obtained from fibrin, silk, casein, etc., and found that those derived from fibrin were most toxic.

*The Secondary Proteoses* or Deutero-albumoses, have been used therapeutically by Lüdke and include the protein fragments that are precipitated by complete saturation with ammonium sulphate after the primary proteoses have been removed by half saturation. The group is an indefinite one and includes a number of fragments evidently of different sizes which have been classified as A, B and C by Hofmeister, as Thio-albumose, Synalbumose, etc.

*Witte Peptone*, which has been frequently studied and which Nolf, Gow and others have made use of for therapeutic injections, consists of a digestion mixture in which albumoses are abundantly found. It is said to be prepared by the digestion of fibrin. From it the primary and secondary proteoses can easily be prepared by salting out in proper concentrations.

**PEPTONES.**—These are further hydrolytic cleavage products soluble in water, not coagulable by heat nor precipitable by ammonium sulphate; they are easily diffusible and give biuret reactions. They differ greatly in toxicity.

**PEPTIDS.**—The simpler compounds of amino-acids, many of which

have been synthetically prepared by linking two or more amino acids—di-peptids, tri-peptids, etc. They are not coagulable by heat, are easily soluble and may still give a biuret reaction.

**The Amino-Acids.**—The amino-acids form the ultimate molecular units from which the proteins are constructed. They are grouped into five classes:—

1. The Aliphatic or Mono-amino, monocarboxylic acids, including glycocoll, alenin, valin, etc.
2. The Mono-amino, dicarboxylic acid group including aspartic acid and glutamic acid.
3. The Isocyclic, amino-acids such as tyrosin and phenyl alanin.
4. The Heterocyclic, amino-acids including histidin, tryptophan, prolin, etc.
5. The Diamino-monocarboxylic acid group with arginin and lysin.

In general the lower split products of the proteins, including the amino acids, are relatively nontoxic and bring about little or no reaction on the part of the patient when injected; the compounds containing the various ring groupings of the carbon atom as well as the diamino group seem, however, to be exceptions. Considerable work has recently been reported by Dale and his associates and by Koessler and Hanke in connection with the toxicity of histamin.

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