

## Address.

IMMUNITY WITH SPECIAL REFERENCE TO  
VACCINE THERAPY.\*

BY TIMOTHY LEARY, M.D.,

Professor of Pathology, Tufts Medical School.

It is my purpose to review hastily the progress of our studies in immunity in order to make plain why that portion of the scientific medical world which has been interested in the *practical* application of immune principles to disease conditions welcomed the work of Wright as opening up a new avenue of approach toward the elucidation of a problem whose solution seemed impossible from the viewpoints which were held at the moment when his work was presented.

The student of pathology learns early in his career that the morphological tissue response to insults is limited to a few fundamental possibilities. Details of the reaction may be infinitely varied, but the basic variations are few, no matter what the character of the injury may be. Further, by artificial stimuli we have not succeeded in adding to the varieties of response which are exhibited against natural stimuli.

It seems to be equally true of immunizing responses to stimuli that the types of response are relatively few.

It should be made clear that the laboratory worker in immunity, when he makes a step in progress, does nothing new or strange. He invents nothing. He evolves no new principles. He studies nature and endeavors to wrest from her the secret of her methods of rendering harmless the parasitic organisms or their products which find themselves in the living animal body. Studies of immunity will be complete when we have laid bare all of these methods. The successful artificial method of attacking an infectious process depends upon as close an imitation as possible of nature's method of accomplishing the same thing.

Practical progress in specific therapy of human infectious processes really began with the discovery of diphtheria antitoxin. First came the demonstration that the diphtheria bacillus produced a soluble toxin; that bouillon in which the diphtheria bacillus had been grown for several days had acquired a definite poisoning power for animals even after the diphtheria bacilli which produced the toxin had been filtered off; that a measurable quantity of this bouillon, or diphtheria toxin, as it is called, would kill a guinea pig of a certain weight. Next came the discovery that an animal into whose body less than a fatal dose had been injected developed after a time the power to overcome what would be a fatal dose for an untreated animal of its weight. The injection of the non-fatal dose of toxin had stimulated the formation of an antitoxin. This antitoxin, produced in various tissues, is delivered into the blood stream, where it is found in the globulins of the blood serum. It was a simple practical problem to produce this substance in quantity in large animals, from whom large quantities of blood

could be removed without harm, and the serum or its globulins made use of to supply the deficiency in antitoxin production in human beings undergoing infection with the diphtheria bacillus, or even to prevent infection in those exposed, by surcharging their tissues with antitoxin and thus making the ground unfavorable for the diphtheria bacillus.

It should be noted that diphtheria antitoxin has no important direct influence on the diphtheria bacillus. It acts solely by neutralizing the toxins of the organism, which, thus disarmed, falls an easy prey to other protective agencies.

The discovery of diphtheria antitoxin led to the hope that similar sera could be produced which would have as happy an influence on other infectious processes. It was soon learned, however, that few other bacteria than the diphtheria bacillus produce a soluble toxin in quantity. A study of infection with the diphtheria bacillus shows it to be an almost pure toxemia. The bacteria are limited to the local lesions in the throat. Here they manufacture their toxins, which are carried in the blood stream to all parts of the body, producing toxic degenerations of the so-called parenchymatous organs and the nerve trunks. The lesions which lead to death are thus produced largely at points distant from the region where the toxins are elaborated. The tetanus bacillus is the only other organism among the important pathogenic bacteria which produces mainly a soluble toxin and whose lesions largely arise at a distance from the bacteria, as in the case of diphtheria.

With the great group of other pathogenic bacteria, the story is a distinctively different one. General processes, when they arise, do so as a result of the invasion of the blood stream by the bacteria (bacteremia), and the organisms are carried to all parts of the body. The staphylococcus, streptococcus and pneumococcus, for example, depend for their activity in great part, not upon soluble toxins, but upon toxins (endotoxins) which are limited to the bodies of the bacteria. The problem in these cases is not the simple one of neutralizing toxins, but the more complex one of destroying bacteria as well.

Investigation has shown that bacteria which enter the blood stream may be destroyed by substances present in the blood serum which produce a digestion — a solution (bacteriolysis) — of the organisms. This phenomenon depends upon the interaction of two substances. The first of these is a specific body, — the so-called amboceptor, — a distinct immune body which may be increased in quantity at will in susceptible animals, just as diphtheria antitoxin may be produced experimentally in quantity. If this body were capable alone of the destruction of bacteria, our problem would be solved. Unfortunately, however, the actual destruction of bacteria (bacteriolysis) is dependent upon the interaction with it of a second body — the ferment which completes the solution of bacterial cells and which is known as complement. Complement is an unstable body, with little resistance to heat, and disappears rapidly

\* Read at meeting of Rhode Island State Medical Society, June, 1910.

from blood serum which is kept. It is present in the blood serum of all living animals, although its quantity may show marked variations. A slight disturbance, such as a headache, may diminish its quantity markedly, and we have discovered as yet no means of increasing the amount normally present to any considerable degree. Hygienic living, with abundant fresh air and good food, will keep its measure at a high par, but even under these conditions slightly untoward circumstances will rapidly lower the amount.

The individual who is undergoing infection with the typhoid bacillus, for example, is producing sufficient amboceptor for his needs. What his blood lacks is complement, and we as yet have no means of artificially supplying this need. Antisera rich in amboceptor may be readily produced, but the real need of the infected individual -- complement -- we cannot provide for.

For these reasons the so-called anti-bacterial or bacteriolytic sera are, as a whole, failures. An apparent brilliant exception, Flexner's anti-meningococcal serum, belongs in a class by itself because of the character of the meningococcus. This organism is one of a group of bacteria which undergo solution readily, probably even in the absence of complement. Rosenow has shown, and our own experience has confirmed this, that the group of organisms to which the meningococcus belongs will undergo solution in any normal serum, even in a serum which has little bacteriolytic influence on other bacteria, and sometimes solution of the bacterial bodies will occur in physiological salt solution. A specific serum against this organism belongs, therefore, in a special class and does not seriously modify the statement that bacteriolytic sera as a whole are failures.

Another method of dealing with infection was suggested by Metchnikoff's observation that the animal body protected itself in part against the invasion of pathogenic bacteria by means of active cell processes. He observed that, in the lower animals, certain infections were held in check or overcome by the action of motile cells, which took the invading bacteria into their bodies and destroyed them by a process of intracellular digestion (phagocytosis). The most active phagocytic cell in the human body is the polynuclear leucocyte. It was shown that the number of leucocytes in the circulating blood could be increased by the use of preparations containing nucleic acid. Substances such as yeast, rich in nucleins, were, therefore, used as a means of combating infection, but without marked influence on the processes.

Thus matters stood when A. E. Wright published his first practical results from bacterial vaccination. From 1892 to 1902, efforts in the direction of specific therapy had resulted in no signal advance. Our study of nature's methods had disclosed no new avenue of approach toward the solution of the problem, and we could not imitate nature successfully along the old ones.

The new facts which Wright brought out were (1) that the cellular destruction of bacteria

(phagocytosis) does not depend solely on cell activity; that before bacteria are taken into the bodies of cells they must be acted upon by substances present in the blood serum (opsonins). White corpuscles washed free from serum are not attracted by bacteria with which they are brought in contact and will not, therefore, show phagocytic activity. The addition of a small amount of normal serum to the mixture of bacteria and washed white cells will be followed promptly by the familiar picture of phagocytosis.

(2) That the injection of suspensions of dead or modified bacteria (bacterial vaccines) into infected individuals would provoke the formation of antibodies more or less specific in character against the bacteria used for making the suspensions. The use of suspensions of modified bacteria in the prophylaxis of disease has been practised since the earliest years of bacteriology. The new step was the demonstration of their value in treatment of infections already established. The response to their injection is indicated not only by the formation of opsonins, but also by the production of other antibodies.

Wright's work has opened up a new world of possibilities in the struggle with infection. It is producing practical results in the treatment of infections which could not be hoped for a few years ago, and it has given the research worker a new basis from which to attack the problems of immunity.

#### THE PRINCIPLES OF VACCINE THERAPY.

It should be said in the beginning that the opsonic index as a measure of the immunity response under vaccination is looked upon in this country as inaccurate. It requires a complicated technique, has many sources of error, and in our experience the results obtained are unsatisfactory. It has a value in the diagnosis of obscure conditions.

Wright believes that a proper therapeutic dose of vaccine in an infected individual is followed by a period of intoxication, accompanied by a diminution in antibodies (negative phase), followed by a stimulation of the immunizing machinery and the production of an increased amount of antibodies (positive phase). Theoretically, it should be possible to bring about the production of surges of antibody production, each wave higher than the preceding one, with progressive beneficial results to the infected individual. Wright, in his early work, insisted that, in order to provoke a positive response to vaccination, it was necessary to inject a sufficient dose to produce at first intoxication (negative phase). Our experience and that of others has shown that the ideal immunizing response can be produced without the toxic negative phase. Physiological doses of vaccines should be followed by an immediate production of antibodies without toxic action.

Wright believes that the individual who is undergoing infection with a carbuncle does not produce sufficient antibodies because the toxins of the staphylococcus are not being absorbed from the local lesions, owing to the disturbed blood vascular circulation and the obstructed lymphatic

drainage of the infected region. Such an individual, however, has general malaise and frequently shows temperature, both of which should be accepted as evidence of toxic absorption. A more reasonable explanation, it seems to me, is that, while absorption of abundant toxic material is taking place, the character of the toxic material is not such as to stimulate the defensive forces. It is possible that there is some selective action in absorption, so that certain beneficial stimulating substances may not be taken up by the lymph stream from the focus of infection.

Another reasonable explanation rests on a belief in the local character of many immunity responses. It has been generally accepted that the immune bodies are produced almost wholly by the blood-making (hemapoietic) organs, and thence delivered into the blood stream. This theory fails to take into account the special immunity which certain tissues exhibit against infection. Most important among these are the muscles. Voluntary muscle is recognized as almost completely immune to tuberculosis, and undergoes infection with pus-producing organisms only after the intermuscular connective tissue has been overwhelmed. We recommend the injection of vaccines into muscle or into the intermuscular connective tissue. The satisfactory response which is obtained, we believe to be due in part to the awakening of the defensive metabolism of the muscle system by a stimulus differing in character from the toxic material absorbed from the local focus of infection.<sup>1</sup>

If the school of vaccine therapy does no more than to call attention to the muscle system as an important factor in the immune mechanism, it will have justified its existence.

Wright believes that an interval of at least seventy-two hours should elapse between inoculations of vaccines because of the toxic-negative phase following each inoculation. Early in our experience it became evident that, with proper dosage, the negative phase could be eliminated. The immunity response began to appear almost immediately following the injection of a physiological dose of vaccine. We have, therefore, shortened the interval between doses markedly, particularly in ugly local or in general infections.

Wright advocated the exposure of the suspensions of bacteria used in making vaccines to 60° C. for one hour for the purpose of killing. The immune response to the injection of vaccines is at least in part a specific one. This may be supplemented by more general phenomena (see staphylococcus below), but the object sought is an increased resistance to the specific organism which is producing the infection in a given case. Such an increased resistance means the formation of antibodies against the specific proteins of the bacterium. Bacterial proteins as well as others lose their specific character by exposure to high temperatures or by prolonged exposure to low

temperature. We have, therefore, gradually shortened the time of exposure of such suspensions to a point where the organisms are just killed. We believe that our greatest contribution to vaccine therapy has been the modification of the killing method. Other methods of killing than by heat (galactose, ether, etc.) have since been advocated, in an effort to preserve the specificity of the bacterial proteins intact.

*Staphylococcus Aureus* vaccine, in addition to provoking the ordinary specific immunizing response, seems to possess the power of stimulating an increase in general resistance. Merriek,<sup>2</sup> who treated a series of infants suffering from furunculosis, calls attention to the fact that the children not only recovered from the boils, but their general nutrition became so improved after treatment that, from a condition of emaciation, they speedily became the best-nourished and most-resistant children in the institution.

#### GENERAL INFECTIONS.

The objections to the use of vaccines in infectious conditions seem to focus themselves against their use in general infections. They will, therefore, be considered here. The general harmlessness of vaccines is indicated by the results in two cases of infection in which, through error, 10 ccm. of *staphylococcus pyogenes aureus* vaccine containing 10,000,000,000 organisms were injected at one time as an initial dose. This is forty times the standard initial dose. In one case no untoward symptoms appeared. In the second there was a temporary collapse, with prompt response to heat and stimulation. There are few powerful drugs in the Pharmacopeia which could be used with such disregard for dosage without serious results.

The most obvious objection to the use of vaccines in general infections is that the patient is undergoing extreme intoxication and that the injection of vaccines will but add to this intoxication. I have called attention to our theory of muscle immunity, and to the fact that physiological doses of vaccines are not followed by a toxic (negative) phase. The dose of vaccine used in pneumonia, for example, contains fewer organisms than will be found in a few out of the myriads of infected air sacs of the lung in this disease. The dosage is so infinitesimal, and its toxic effect is so slight, if any, that it is not measurable. As evidence that even much larger doses are at least harmless, I might cite the case of a child of seven years undergoing an infection with pneumonia, with a temperature of 103 and extreme meningeal symptoms, into whose body was injected as an initial dose, 8 ccm. of pneumococcus vaccine containing 1,600,000,000 pneumococci. The standard dose for adults is 8 minims, or 100,000,000 pneumococci. This child receiving sixteen times the adult dose of vaccine not only did not show harmful results, but began to mend shortly following the initial injection and recovered under daily injections of several times the usual adult dose. A second child with pneumococcus meningitis showed prompt diminution

<sup>1</sup> Since this paper was read, Theobald Smith, in a paper on "The Experimental Basis for Vaccine Therapy," read before The Massachusetts Medical Society, June 8, 1910, called attention to the possible local character of immune body production, and suggested vaccination in different sites as a means of awakening these local mechanisms.

<sup>2</sup> Ann. Gynec. and Pediat., September, 1908.

in the number of pneumococci in the cerebrospinal fluid, and sharp amelioration of symptoms accompanying the use of four to eight times the standard adult dose of pneumococcus vaccine. Death occurred from exhaustion, the meningitis having followed a series of children's diseases with bronchopneumonia,

Another objection offered to the use of vaccines in general infections is that vaccines stimulate the production of bacteriolytic substances and that these substances may kill many bacteria and set free their toxins, thus overwhelming the body with toxic products. Flexner's anti-meningococcic serum is a bacteriolytic serum about whose value there is little question. It is injected into the subdural space of children who are suffering from extreme intoxication with the meningococcus and its products in a region which is most sensitive to these products. Its injection is followed by the immediate action of its bacteriolytic substances on the meningococci with which they come in contact. Examination of the fluid shows a prompt and extreme diminution in the number of meningococci, and yet I have never seen reported harmful results related to the sudden setting free of their toxins. Following the injection of vaccines, the theoretical evolution of bacteriolytic substances, if occurring, must take place slowly and gradually. There is not an explosive setting free of these substances such as the injection of meningococcus serum brings about, and the effect, if any, must be less than that shown in meningitis, which is practically negligible.

It may be argued that Flexner's serum contains anti-endotoxins capable of neutralizing the toxins of the meningococcus when set free. If this is true, it is the first practical anti-endotoxic serum which has been produced (Besredka's anti-endotoxic typhoid serum has only experimental interest) and Flexner makes no claims of anti-endotoxic properties. Even though such claims are made, the prompt recovery of a child into whose subdural space normal horse serum was injected in an emergency when Flexner's serum could not be obtained would suggest that danger from products of bacteriolytic action is not serious.<sup>3</sup>

A third objection is that patients undergoing infection are in an anaphylactic state; are, therefore, hypersusceptible to intoxication. With chronic infections such as tuberculosis this danger apparently exists, and for that reason I believe the use of tuberculin in treatment should be carried out with extreme care. We have never seen evidence of its existence in the acuter conditions produced by other bacteria. It takes time for the establishment of anaphylaxis, and the general infections with their sudden onset should be largely free from such danger. Anaphylaxis is a purely theoretical danger, as is evidenced by the infrequency of serious results following the use of diphtheria antitoxin. If guinea-pig experiments with horse serum gave a true picture of what was to be expected in human beings, the use of diphtheria antitoxin would be so limited

on account of anaphylaxis that its value would be very questionable. As I have said elsewhere, theoretical considerations of this sort must yield to the facts of experience.

#### DISTINCTION BETWEEN GENERAL AND LOCAL INFECTION.

The old belief in bacteriology was that there was a sharp dividing line between general and local infections. More recent work has demonstrated that such a line does not exist. Every case of typhoid fever is a general infection, as is every case of pneumonia, endocarditis, meningitis and most of the acute septic processes. It has been demonstrated that every case of erysipelas starts in as a general infection. Recovery from these conditions is brought about, first, by the localization of the infection and then by the destruction of the bacteria in the local focus.

In streptococcus general infections French workers found that the injection of turpentine into skeletal muscle, if successful in provoking a local abscess, was associated with the focalization of the infection, which could then be handled as a local process. If the patient's condition were such that local abscess formation did not occur, then the treatment was not successful.

Our grandfathers, probably with the same end in view, thrust setons through skin, subcutaneous tissue and muscle with apparently similar results.

Some of our results with general streptococcus sepsis were illuminating in much the same direction. We were given opportunity to treat cases of puerperal sepsis in which all clinical expedients had been exhausted and in which the outlook was hopeless. In a number of these cases a prompt drop in temperature followed the exhibition of vaccine. In this group I am somewhat skeptical as to the influence of the vaccine, since other factors may have played a part. In many of the other cases there was a progressive forcing downward of both pulse and temperature, which reached normal after several days. In certain of these cases local formation of pus, either in the uterus or else in muscle or subcutaneous tissue, occurred from one to three days after the temperature had reached normal. The further treatment of these cases consisted in the simple problem of caring for a local infection.

The localization of a general infection following the injection of turpentine into muscle by the French, the introductions of setons according to the older surgery or the injection of specific vaccines according to the newer procedures, first drew our attention to the apparently important part which local defensive mechanisms, and notably muscle, played in increasing general resistance.<sup>4</sup>

It is not my intention to speak of the use of vaccines in pneumonia until we have carefully collated the data obtained from reports of work

<sup>4</sup> I do not want to be misunderstood as claiming that we have solved the problem of streptococcus general sepsis. We believe that we have saved many cases of puerperal general sepsis which otherwise, according to the best views of able practitioners and consultants, would have died. Some cases, notably those whose resistance was gone, have died. In cases where the resisting mechanism was still capable of stimulation, the use of an autogenous vaccine killed at 60° C. for fifteen to twenty minutes, and injected at frequent intervals in physiologic doses, has furnished remarkably good results, and we have never seen evidence of harm.

<sup>3</sup> Personal communication, Dr. S. P. Beebe.

during the past year. We have furnished pneumococcus vaccine for about fifteen hundred cases, but in spite of the fact that we made the reports so simple that a few minutes would suffice for recording the desired data, the return of these reports is slow. The evidence seems to predominate that this vaccine is a distinct addition to our armamentarium.

#### LIMITATIONS OF THE VACCINE TREATMENT.

Vaccine treatment in surgical conditions does not do away with the necessity for intelligent surgery. In an accumulation of pus the opsonins and other antibodies which are formed in response to bacterial vaccination cannot be delivered from the blood stream into the pus. In thick pus currents are sluggish or absent and the transmission of antibodies into the central part of the mass of pus must be interfered with. Contact with the bacteria is prevented and, therefore, the organisms are unaffected. It is essential that drainage be established. If this is done, the bacteria along the granulating wall will be quickly destroyed and healing be more rapid than surgical measures alone could bring about. Vaccine therapy does not supplant, but supplements, intelligent surgery.

With infections in certain locations, particularly along some mucous surfaces, vaccine therapy is less successful than elsewhere. Gonococcus vaccine, for example, has little influence on urethral infections in our experience, but a freshly prepared gonococcus vaccine made from first cultures from fresh cases gives such prompt and constant results in gonorrhoeal rheumatism that we are led to doubt the diagnosis in cases which do not respond. Our doubts have been justified in all cases which did not respond in a considerable series.

In infections of the kidneys, where there is a local irritant in the form of a stone, or where drainage is interfered with, vaccine treatment has little value. If the colon bacillus is the infecting agent, intoxication will be relieved and fever eliminated, but local infection will persist.

In the bladder, if residual urine is constantly present, vaccine therapy is only palliative, since the chronic irritation of the bladder mucosa by products of the saprophytic bacteria usually present will favor the continuation of the process.

In bacteriuria, vaccines have little value. Bacteriuria is marked by the growth of organisms in the urine, as in a culture medium. There is no infection. The bacterium and the human being are growing in harmony. No means of breaking this symbiosis has as yet been discovered for most organisms. Infection, if it exists, can be overcome, but the symbiosis persists.

#### NECESSITY FOR RESISTING ABILITY.

Diphtheria antitoxin confers a passive immunity. It requires the patient only to furnish a circulation for its distribution. When it comes in contact with diphtheria toxin, it neutralizes it without assistance from the patient. The defensive mechanism of the patient is left free to cope with the diphtheria bacilli at the point of infection.

Bacterial vaccines require the active co-operation of the patient. Vaccines, as far as we know,

accomplish nothing directly except to stimulate the lagging immunizing machinery to produce needed antibodies. It is, therefore, essential that the defensive mechanism be in condition to respond to this stimulation if good results are to be obtained. For lack of this preparedness, fulminating cases of streptococcus peritonitis, for example, in which the septic absorption is extreme, do not usually respond to treatment, while slower infections do.

#### PRACTICAL APPLICATION.

It is not possible nor desirable to go into detail about practical procedures in this rather lengthy paper. Suffice it to say that the group of infections for which the average practitioner desires to use vaccine therapy, while comprehensive, is due to the activity of relatively few organisms. *Staphylococcus* vaccine is now accepted as the standard method of treatment of local conditions due to this organism. In general infections results are less satisfactory because, I believe, such a general process is usually a pyemia, and the organisms in a pyemia are contained in masses of clot and less accessible to the antibodies which may be formed.

Of *streptococcus* general infections I have spoken. Among local infections, erysipelas responds in most cases with promptness. This is particularly true if an autogenous vaccine can be obtained. Local septic processes also respond promptly.

The empiric use of vaccines made from autogenous throat cultures, and containing usually a mixture of the pneumococcus and streptococcus, has given usually prompt relief of pain and a bettering of other symptoms in a large percentage of the cases of rheumatism treated.

The treatment of the associated infection in tuberculosis with autogenous vaccines in which the streptococcus and pneumococcus usually predominate is accompanied by diminution of temperature and relief of cough and night sweats, followed by increase of weight.

*Pneumococcus* and *gonococcus* processes have been mentioned.

The frequency with which *B. coli* is an infecting agent has only been fully appreciated since vaccine therapy has been inaugurated. The colon bacillus may give rise to marked toxic symptoms from a relatively slight infection. Such intoxication can be relieved usually within a few hours. Genito-urinary infections due to this organism have been considered. The response in bladder infections, where well drained, is rapid and permanent where re-infection can be guarded against. In typhoid fever the so-called exhaustion which arises in the late stages and which leads frequently to a fatal issue is apparently due to *B. coli* infection. An autogenous vaccine made from the feces has in three cases with us been followed by a prompt disappearance of the septic temperature and rapid progress to convalescence. In membranous colitis an amelioration of symptoms persists while the vaccine is used, but prompt relapse usually follows its withdrawal. *B. coli* vaccine prepared from the urine of cystitis asso-

ciated with rheumatism or rheumatoid conditions has not only cleared up the cystitis, but has also relieved the rheumatoid symptoms promptly in a small series of cases with us. *B. coli* vaccine should always be prepared directly from the patient's organism and should be used in small doses. The initial dose should not be more than 25,000,000, cautiously increased.

**Tuberculin.**—No final judgment of the value of any agent used in the treatment of tuberculosis can be made unless its practice has been followed for many years. I am, therefore, only hazarding an opinion of the value of tuberculin from our limited observation. I believe that tuberculin in proper doses is a valuable addition to standard methods of treatment. Its use, however, is associated with dangers which make extreme caution necessary in its exhibition. Wright's method, which calls for an extremely small dose at weekly intervals, seems to eliminate all dangers of over dosage.

I hope that the time is not far distant when local laboratories will properly develop the field of vaccine therapy. The observer in this field requires an accurate and extensive knowledge of the small group of organisms which play a part in most infectious processes. With this mental equipment a knowledge of the technic of vaccine production and therapy can be quickly developed. There is no reason why autogenous vaccines cannot be produced in the larger hospitals and medical centers of the community. I look forward to the day when an equipment in this direction will be expected of the local pathologist and bacteriologist.

Vaccine therapy is in its infancy. It is but a step in progress toward the specific therapy of infectious processes for which the medical world has been anxiously waiting. I trust that I have made clear my reasons for believing that, through the new viewpoint it has opened, a way to the solution of these problems may be made possible.

## Original Articles.

### TYPES OF GRAVES' DISEASE.

BY J. G. MUMFORD, M.D., BOSTON.

THE types of Graves' disease are so various, and the special symptoms, or lack of symptoms, so puzzling, that it is well for a student of the subject frequently to compare cases, especially that he may bring home to himself the possible and serious outcome of conditions which often appear trivial and more often are obscure. Frequently it happens that the frank, acute cases, with the classical symptoms, are cured by any treatment, and by no treatment even. Sometimes it occurs that a case apparently trifling, perhaps running an easy, chronic course, suddenly becomes worse and dies in spite of all treatment.

Here are two dissimilar cases, a typical case and an atypical case, both of which occurred in my practice, both of which caused me the greatest anxiety and taught me new lessons regarding the nature of this interesting ailment.

Case I was that of Mrs. A. S., a woman of forty-two. She had behind her a long surgical history, — operations for salpingitis, for retroperitoneal cyst, for ovaritis, — but in spite of these serious diseases and operations, which occupied many years of her younger life, she came out strong and vigorous. At the age of thirty-seven, however, she consulted her physician for what appeared to be a trifling heart lesion, for she found herself troubled with occasional dyspnea on exertion. Her physician discovered a slight mitral leak and some dilatation of the heart. Careful treatment and prolonged rest resulted in no benefit; gradually there developed further a constant distressing dyspepsia, pain and nausea after eating and a state of continual apprehension. These symptoms persisted for two years, when there developed further a mild, bilateral tremor of the fingers. At this stage she consulted me, on the advice of her physician, and I was able to suggest the diagnosis of exophthalmic goiter. Even so, the diagnosis was by no means assured, for no enlargement of the thyroid was evident, nor were there marked eye symptoms, while the heart rate rarely went above 80. We continued to treat her as a cardiac case only — bearing in mind the possibility of Graves' disease — for another year, when within a month there developed a series of characteristic symptoms: the thyroid gland became enlarged, with a typical thrill; the eyes gradually became prominent, with lagging of both lids and widening of the palpebral fissure; and tachycardia became pronounced, the rate of the heart ranging between 110 and 130.

Here was a case which, in spite of its gradual onset, seemed suitable for immediate and vigorous medical treatment. Accordingly, we instituted the use of hydrobromate of quinin, neutral, in 5-gr. capsules, three times a day, and continued the medication without intermission for fifteen months. During the early months of treatment the patient experienced great relief; her apprehension vanished, her thyroid tumor became somewhat smaller, the heart action became slower and her general sense of improvement marked. Such was her state twelve months after the beginning of the quinin treatment. She was not well, however, and her condition of instability became especially apparent at that time through the accident of a serious grief; a favorite sister became ill, and, after a month's extreme suffering, died, under the constant watchfulness of our patient. The strain and anxiety of this experience renewed at once, and markedly, the exophthalmic symptoms. Within a very few weeks, from the state of quiescence I have described, all her discomforts reappeared; the eyes became prominent and anxious, with their associated abnormal lid phenomena; her tachycardia returned; the heart became irregular; dyspnea became extreme; she was troubled with a constant diarrhea and distaste for food; profuse sweating became pronounced; the tremor returned in force; and the right lobe of the thyroid rapidly doubled in size.

Now the case presented all of the typical