

not considered as essential for the transmission of bacteria, and Chambrelent is of this opinion, for in his experiments on female rabbits he never found that organ pathologically altered, but Malvos believes that in order that a mother can directly inoculate the fetus with micro-organisms there must be a lesion of the placenta, while Schmorl and Birch-Hirschfeld found small granulations and Koch's bacilli in the placenta of tubercular guinea-pigs.

Last summer Charrin and Duclert reported a series of experiments, showing, on the one hand, that intoxication by the toxins, and, on the other, external poisonous material, as lead, mercury or substances derived in certain cases from cellular life (as lactic acid) aid the passage of bacteria through the placenta in a variable degree. According to these writers, the glands which are often excellent fortresses are after a time destroyed by the secretions of the bacteria, as, for example, the kidneys, the organisms then penetrating, going from the capillaries into the tubuli, especially after the epithelial structures are deteriorated. And they conclude that at present they would say that the toxins act more on the cells of the organism than on the virus itself. Rémy examined the placenta of phthisical women who had had premature labors, and found their uterine surfaces whitish in color while there was a degeneration of the decidual cells.

Consequently, I think it safe to hold that in some cases tubercular endometritis is consecutive to a pulmonary infection, and may interrupt a pregnancy as well as producing lesions of the placenta, and by this means infecting the fetus.

## Original Articles.

### THE ETIOLOGY OF DIPHTHERIA AND THE USE OF ANTITOXIN.<sup>1</sup>

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THE etiology of diphtheria may be said to be so firmly settled at the present time that it is not necessary to rehearse the proofs that have been brought forward to demonstrate it; but the difference between diphtheria and those processes that resemble it do not seem to be any too clearly impressed upon the minds of the general profession.

The recent advances in our knowledge of the infectious diseases have not met with ready belief, possibly because of a lack of understanding of the changes that these advances impose. It is not an easy matter to learn that not all processes presenting similar clinical pictures are due to the same cause; and it appears to be equally difficult to bear in mind that entirely different series of phenomena may be produced by the same infective agency, acting on individuals with different personal peculiarities, and even in the same individual in different localities.

Now the recognition of these facts and the bearing them constantly in mind is absolutely necessary for understanding the present position in regard to the etiology of diphtheria. This disease is no longer to be considered to be one set up usually in the throat, to be detected by a certain definite chain of symptoms, but the name must be confined to that series of changes

in which the bacillus first seen by Klebs, and first studied by Löffler, is active as a causal factor.

The history of the long series of experiments by which this has been established would be tedious to rehearse in this place, but since the very beginning, with the publication of Löffler's work, the evidence has been accumulated, until now there can be no doubt of this fact, that the bacillus frequently called by his name is the cause of by far the larger number of cases having the clinical aspect of diphtheria, and that, therefore, this name should be given to the processes set up by this bacillus and to none other.

At the same time, it should be very carefully borne in mind that there are other changes, occurring not infrequently, that resemble diphtheria as thus defined very closely, and that at present are indistinguishable from true diphtheria by any practicable test but that of the cultural examination. Practically such cases may be just as severe and probably just as infectious as true diphtheria, although not usually so, so far as my knowledge extends; but this fact does not in the least lessen the importance of an exact diagnosis; it should rather serve to arouse an increased enthusiasm in the study of what these other processes are.

The facts being these, it is natural that the question should be asked: "What difference does it make if my patient has a 'bacillus' sore throat, or any other kind of sore throat, if the clinical picture be the same?" But such a question can hardly be repeated in earnest after the events of the last year. Of course, it makes as much difference as it does whether it be true tuberculosis or not in a person with a destructive process in the lung.

We are supposed to be entering upon an era of "specific" medication based upon the knowledge gained by our studies of the bacteria and other micro-organisms; and surely, if specific treatment is to be carried out, a specific diagnosis must go hand in hand with it. This may appear to be an unnecessary reiteration of facts known to us all, but these facts are not always borne in mind—the best example of what I mean being found in connection with the disease under discussion to-day. It is the custom abroad, in many of the hospitals, to inject *all* cases of sore throat with the antitoxin of diphtheria, without waiting for the result of the cultural diagnosis; and from one point of view, this method of procedure is perfectly justifiable and has been adopted at least in some instances in this country. It is right to do this, for the reason that all experience and analogy show that the earlier the antitoxin is used the better the results; and the claim is still made in Berlin that no case has been lost when the injection has been made on the first or second day of the disease—of course, after that time the mortality increases. If, as it is supposed, the antitoxin has no deleterious effect in non-diphtheritic cases, then, of course, no risks should be run by delay in its administration. On the other hand, it is difficult to see how the antitoxin can have had a beneficial effect in cases of recovery in non-diphtheritic cases in which it has been used. It either is or is not a specific against diphtheria, and so far as we yet know it has no specific action upon the bacteria or their products that are concerned in the production of the non-diphtheritic processes in the throat. We must conclude, therefore, that in the cases in which its use has apparently been beneficial the results are merely coincidences, or else true diphtheria was present after all.

<sup>1</sup> Read at the Annual Meeting of the Massachusetts Medical Society, June 12, 1895, and recommended for publication by the Society.

This conclusion seems necessary, for the reason that the whole of "serum-therapeutics" depends upon it, for which statement some explanation may be found in the lines of modern research. These are almost wholly towards the question of immunity. What this is supposed to be it is not necessary to discuss at length, but we may recall that there is a "natural" and an "acquired" form; the former existing in certain races of animals or in single individuals of a race, rendering them insusceptible to the attacks of certain infectious diseases. The latter is the insusceptibility to a second, acquired by individuals who have passed successfully through a first attack of an infectious disease, and is of very varying duration.

Now it has been known for some time that this acquired immunity may be artificially induced in animals by varying procedures connected with manipulation of the bacteria or their products, or, occasionally of the animals themselves. Of course, the discovery of the possibility of successfully accomplishing this object in a manner free from danger was, to the medical man, like a burst of sunlight through a fog to the sailor; and the literature of modern experimental medicine is largely made up of the record of efforts to this end. Thus far, diphtheria is the disease in which these efforts give the greatest promise of success, but at the best this success cannot be said to be complete until some better means of preparation and administration has been devised for the remedy used.

The exact methods by which the antitoxin is produced will be treated later; the consideration of the steps that have led up to its use at all may, however, be of interest, and these steps include all of those that have been taken in the attempts to secure the artificial immunity just spoken of.

The theories of the causes of immunity are many, and we do not yet know whether one or all of them are to be considered active in producing the result; the truth appears to lie between the extremes, and the facts seem to show that immunity can be explained only by a combination in varying degrees of activity of the several causes that have been suggested, and that at one time one of these is the more prominent, and at another time, or in other individuals another takes the more prominent part.

The important theories that have been advanced to explain the production of immunity may be briefly stated as follows: First, and especially upheld by the French, is that of "phagocytosis," due, so far as its elaboration is concerned, to Metschnikoff. According to him, the phagocytic power is exercised by the leucocytes, of which he distinguishes several varieties. The *lymphocytes* are small leucocytes with a large nucleus, that are surrounded by a small quantity of protoplasm; they are very numerous in lymph, and present all degrees of shape in their transformation into large leucocytes called *mono-nuclear leucocytes*, whose nucleus is frequently in the shape of a kidney or bean. The *eosinophilic leucocytes* of Ehrlich have a lobulated nucleus, and their protoplasm contains certain granules that stain intensely with the acid aniline dyes, especially with eosine; they are supposed to develop at the expense of the bone marrow. The most numerous of the leucocytes are called *polynuclear*, for the reason that their nuclei are most frequently separated into several parts by exceedingly fine lines of division; their protoplasm contains granules that most frequently stain with a mixture of the acid and

basic dyes only, and they are therefore often called *neutrophilic* leucocytes; they develop in the blood from the small cells furnished by different organs. All leucocytes throw out protoplasmic appendages that enable them to move, but not all of them are capable of englobing foreign bodies, that is to say of "phagocytosis"; this property belongs only to *mono-nuclear* and *neutrophilic* cells, and permits them to englobe the bacteria with which they find themselves in contact, and these bacteria are often englobed in the living condition. This property of englobing and destroying virulent bacteria has been said by one set of observers to be the cause of immunity; but many experiments, those of Charrin especially, have shown that there occur substances, in the fluids of immunized animals, that modify the bacteria and their action, independent of the presence of the leucocytes, showing that phagocytosis cannot explain all the phenomena of immunity at all times.

The bactericidal power of the blood serum is another of the causes of immunity that has been put forward. Grohman and Fodor first demonstrated that when bacteria were grown in the blood their vitality was diminished, but the final result of the work of Buchner, Ogata, Lubarsch, Nissen, Hankin, and many others, is to show that the destruction of the bacteria in the serum is much more active out of the body than in the vessels; if the cells and proteid materials of defibrinated blood be allowed to settle, the bactericidal power is found in the sediment and not in the serum; when the leucocytes remain intact outside of the body, the serum is not bactericidal, but becomes so when the white globules are destroyed. As a conclusion from all the work upon this line of research, it would appear that the phagocytes destroy the bacteria by digesting them, and that the feeble bactericidal power of the living serum exists as a result of the breaking up of some few phagocytes in the body (Cheron).

Third, and most important to our present subject, is the theory of the "antitoxins," claimed by the French to be a rejuvenation of the old theories of Chauveau. These antitoxins have been worked out for but a few diseases at all, and farthest in diphtheria, and we do not even yet know precisely what they are.

One theory of their formation is this: The bacteria produce, during their growth, a new compound, a toxine, which is hurtful in varying degrees to the tissues in which it is formed, and which excites a new functional activity in the tissue cells. This new functional activity results in the secretion by these cells of a new product that has a neutralizing effect upon the toxine. This process goes on in all cases of diphtheria, for example, and as the formation of the neutralizing substance progresses more rapidly than the production of the toxine, recovery occurs; and, on the other hand, if the toxine is produced sufficiently to prevent the appearance of the new functional activity of the cells, recovery does not occur. Precisely how the neutralizing effect of the antitoxin takes place is not known. It is not by a direct chemical action, at any rate in tetanus, for it has been shown (Buchner) that a prolonged contact of the tetanus toxine with the antitoxin does not destroy the former. It would seem, therefore, that these two substances are antagonistic only in the sense that one — the antitoxin — deprives the tissues of their receptivity for the toxine. However that may be, the experimental evidence shows conclusively that it is possible to produce an immunity

to an infectious disease by artificial means, and that this immunity may be produced in various ways.

The attempts to secure immunity have been carried on for years; they were begun before the object aimed at was even fairly understood. From the substitution of a milder disease for a malignant one of the same type, as is done in vaccination against small-pox, the chain of experiments has extended through the use of the various forms of attenuated virus and bacterial products to this last one which gives so much promise. The use of the serum containing the antitoxines is but the natural growth along the line in which experiment has been directed since the study of the bacteria began under modern conditions, and the whole history is better illustrated in the case of diphtheria than in any other disease. Beginning with Löffler's cultivation of the bacillus (1883), our knowledge of the etiology and management has steadily advanced. Roux and Yersin marked an epoch by their classical monograph, clearing up many things from a clinical standpoint and emphasized by their hospital statistics the need of a greater reliance upon the bacteriological diagnosis. These authors, with Frosch, showed that the bacilli are not always confined to the seat of the local manifestations, but are frequently distributed, although often in small numbers, throughout the internal organs. Brieger and Fraenkel (1891) began the special study of the toxine. Wassermann and Proskauer (1892) apparently isolated it, although Fraenkel failed to secure any immunizing results with the dry powder of this substance. Behring began in 1891 his investigations on diphtheria, which apparently led the way to what has already been spoken of as a "System" of Blood-Serum Therapeutics. His enthusiastic work, together with that, among others, of Wernicke, Aronson, Ehrlich, Kossel, Wassermann and Roux, have led us through the slow and dangerous immunizing of the lower animals, by means of the cultures and toxines of the bacillus of diphtheria, to the rapid and safe immunity following the use of the antitoxin contained in the serum of immune animals.

It is this point that we have now reached; that we have come thus far, all the evidence tends to show, although no one should suppose for a moment that there has been discovered a remedy for all stages of the disease. Nor should the general profession feel that the end is reached; much more is to be done before it can be said that more than a beginning has been made. We know that the serum of immune animals, and even the milk of some of them, possesses this mysterious property of neutralizing the effect of the poison elaborated by the bacillus, but we hardly know anything more. This is notably the case as far as regards the dosage and the methods of testing the strength both of the toxine and of the antitoxin. The standard, or rather the standards of the Germans appear to be unnecessarily complicated, and my personal experience has been such as to emphasize the difficulty of carrying out the comparatively simple method of Roux. Because of what I believe to be the unavoidable variability of the standards employed, there cannot be any exact dosage given, and it is fortunate that a few cubic centimetres in excess does not make any practical difference, so that, given a specimen of antitoxic serum, a slightly larger quantity than that directed may be used with safety. Something may be hoped for, in the direction of exactness, by the method of evaporating the serum to dryness and

then testing its power, but even this is but a makeshift, as compared with the chemical accuracy possible in the management of the known compounds. We must look to chemistry for aid in this direction, and some method of extracting the antitoxin must be devised before we can face the problem of exact dosage with any prospect of its proper solution.

The results of the practical application of the facts that we have learned will be stated by those following me this morning, but there are a few points that I may speak of before closing.

As is fairly well known, the bacteriological diagnosis of diphtheria has been made for the general profession for some time at the Harvard Medical School, in the bacteriological laboratory. For over a year it was done by us—mainly by Dr. McCollom—as an experiment, for the purpose of testing its value and the desire for such an investigation by the medical profession. Systematic work of the kind, however, was first done in this vicinity at the Boston City Hospital, and of course is still carried on there. Since last fall we have acted for the Boston Board of Health, and for many of the communities lying in close proximity to us, and, so far as we can judge, there is a constant increase in the importance attached to this method of diagnosis. Since the first of November, 1894, there have been sent in nearly five thousand cases for diagnosis, and in the neighborhood of one thousand for re-examination. Of course, all of the primary examinations are voluntary on the part of the physician, and would hardly have been sent if there had not been much reliance placed upon the method. We are not able to follow each case, but where inquiries have been possible the results have even surprised ourselves by their accuracy. Of course nothing is infallible, and here is no exception to the rule, but there has not yet been given evidence to show that this is not by far the most accurate method of diagnosis at our command. Whether due to the wide use of this method and the consequent detection and isolation of otherwise unsuspected cases, or whether due to this in connection with the systematic inspection of the schools, certainly the great epidemic of diphtheria in Boston this last winter has diminished in a very gratifying manner. The disease was at its highest at the beginning of the systematic use of the bacteriological diagnosis and the inspection of schools, in December, 1894. From that time, month by month there was a steady fall, sharper than occurred in previous years, until the slight rise that apparently always appears in May just before the schools are closed for the summer.

Of the inspection of schools, it may be said that it has happened more than once that a child has been sent home for a slight sore throat, and that cultures have shown the presence of virulent bacilli from one to three days before the clinical diagnosis of diphtheria was in any way justifiable, so that it would seem advisable for the cultural diagnosis of diphtheria to become even more a matter of routine than at present.

The preparation of the antitoxin of diphtheria is a matter of so much importance, requiring so much special knowledge, that we are especially fortunate in this State in having the supply under proper control; that for the City of Boston is at least in part provided for by the City Board of Health,—that for the State outside of the city by the State Board of Health.