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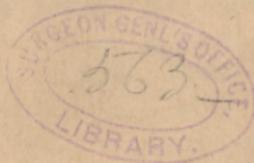
MODERN DIFFICULTIES IN
BACTERIOLOGICAL DIAGNOSIS.

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At a time when in the popular estimation bacteriology is showing itself to be of greater and ever greater import not only in matters of health and disease, but also in the very commonest commercial relations of every-day life, and when the world in general seems to be becoming rapidly convinced that the microbe is at the bottom of everything ; when, in fact, bacteriology has already made an ample apology for its existence, it is, I think, well that occasionally one of us, not from a sceptical spirit, but because of the very strength of his belief in the importance of his science, more especially in its relationship to public health, should pause, and should, as a bacteriologist, point out that matters are not quite so settled, that in fact everything is not quite so surely established as in the opinion of very many it would seem to be.

Taking into account the extraordinarily large accumulation of facts that we now have concerning the bacteria, it is wonderful to think that to all intents and purposes the advance of bacteriology has been synchronous with the

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scientific lifetime of so young a man as I am. There is scarce one present here but can remember the days of ample doubt as to the pathogenic properties of any of the bacteria ; scarce one but can remember the time when Pasteur's wonderful series of observations upon anthrax and the bacillus of anthrax hardly received credence. From that period one saw passing days of gradually lessening doubt, until Koch's wonderful investigations into the bacillus of tuberculosis made men rush to the other extreme, made them absolutely sure that whether the microbe was discovered or no, specific microbe exists for every febrile disease, and for a great number of non-febrile diseases. Now, at the present time, there is among bacteriologists, among those deeply read and acquainted with the subject, as it were a backward swing of the pendulum, to a certain extent. What I mean is that, largely through the teaching of the German school of bacteriologists we had, but a few years ago, come to look upon every disease in which a definite microbe had been discovered, as being due to the presence within the organism of some microbe whose characteristics were absolutely sharply-defined. There was, for example, an absolutely specific microbe of cholera, possessing constant properties, constant peculiarities of growth on various media and constant chemical reactions of part of its products, with constant development of special ferments. There was a sharply-defined diplococcus of pneumonia, a bacillus of typhoid that could not be confounded with any other microbe. And so on with regard to all the important diseases whose germ has been discovered.

Well, I do not wish now to say that this is false ; all that I wish to do in this short paper is to impress upon you the advisability of crying " Halt " before we unreservedly stand to this belief, and it is of especial importance to the members of this Association that the advisability of deliberating long and carefully should be kept in mind ; inasmuch as it is just in relation to some of the most wide

spread and epidemical microbes that we have at the present moment the greatest difficulty in regard to the exact bacteriological diagnosis. That these microbes, by their presence and growth in the system, causes disease no sane [and competent bacteriologist has the smallest doubt, but we have before us in relation to typhoid, cholera and diphtheria, not to mention other cases, a series of problems that are as yet unsettled. The right solution of these problems is, from the point of view of the public health officer, of vital importance. As yet I cannot regard these problems as having been fully solved or nearly solved ; and in this view I believe I shall have the support of my fellow-bacteriologists.

The main problem before us at the present time is in relation to the determination of species. Are we to conclude that there are, it may be, several closely allied species which are capable of inducing the main symptoms of any given disease, or are we to regard the several slightly divergent forms which may be gained from different cases of what clinically we recognize as a single disease as but varieties or races of one species which have obtained more or less permanent characters setting them off from the type ? What, in short, are we to regard as the limits of variability ? Apart from a constant recurrence to experimental inoculation (which is not always possible) how are we surely to recognize the pathogenic nature of the form we isolate from cases of disease ?

Take, for instance, what is found in connection with typhoid ; no one in our days, who has made actual observations, has the slightest doubt as to the cause of that disease ; every one is agreed that it is due to a bacillus, having, on the whole, well defined characters, if once we obtain the bacillus from the body of a patient in a fairly early stage of the disease. No one, again, doubts but that typhoid spreads through the water, through contamination of the water supply, but now here is the difficulty. If we examine, in the first place, the water supply, supposed to be contaminated, in case after case we may be successful in

discovering on suitable media of growth colonies, or growths, which closely correspond to typhoid bacilli ; or, again, if we examine the stools of the patient supposed to be affected by the disease, there again we may, among crowds of colonies presenting but a slight divergence from the characters usually regarded as typical of the bacillus of enteric fever, find some few colonies only distinguishable by the most delicate tests, but still not quite conforming to the type, and the question is, are those colonies truly those of the typhoid bacillus, or do they represent some closely allied species ? For myself I scarcely see how it is possible to give a positive answer in either of these cases. It is true that in other diseases the point can be settled by experimental inoculation into animals ; in enteric fever, however, unless one is successful in gaining cultures of the microbe direct from the human organism from a typical case of the disease and employing them while they are still young, inoculation into animals is of no effect. Then there is another side to the question. Suppose that one repeats the series of experiments made by Babes, and carefully examines the peculiarities of the growths obtained from different cases of undoubted typhoid at different periods of the disease, then it is possible by these means to separate out quite a large number of cultures, whose general properties, it is true, correspond with those of the typical *Bacillus Typhi* of the text-books, but which at the same time in minuter characters differ from the type and from each other to quite the same extent as do the cultures of doubtful import found in supposed contaminated water and in the fæces of suspected cases. I do not mean to say here that in the majority of cases of typhoid one comes across any marked divergences from the type, but in a large number of doubtful cases it is that one is most likely to have, and that one most frequently does have these slight cultural divergences, and the question is what is the conclusion at which we are to arrive. Are we dealing with varieties of the bacillus of typhoid, or are these wholly different and non-pathogenic species ? What is to be our diagnosis ?

Or, take again cholera? Every one, I suppose, is acquainted with Cunningham's remarkable declaration that out of sixteen cases of cholera at Calcutta, the home of the disease, he was able to isolate no less than ten different spirilla resembling each other on the whole, but nevertheless in his belief presenting such clear and constant distinctions that he classed them not as varieties but as species.* Thanks to Professor Welch, of the Johns Hopkins University, I had last year a series of more than half a dozen growths taken from patients suffering from undoubted cholera, who had come from Europe in different ships to the port of New York during the last cholera epidemic. These cultures had been isolated by that able bacteriologist, Dr. Dunham, and certainly each separate case presented some little difference either in rapidity of growth, in amount of pigmentation, in morphological characters of the spirilla separating them off from Koch's type. Case after case might be recorded of these divergences on the part of growths of the cholera spirilla from different quarters, the most noticeable being those recorded by Sanarelli and by Metchnikoff in connection with spirilla taken from various cases in the neighbourhood of Paris. The difference between these various growths are as great as are those between Koch's typical spirilla and the spirilla obtained from water in regions where no true cholera has occurred. Only quite recently, for instance, an epidemic not of cholera but of diarrhoea has been described as occurring at Lisbon, in which spirilla closely resembling the true spirillum of cholera has been isolated. Here again, what is the conclusion that has to be drawn? How is the health officer at any point of landing to give an absolutely certain bacteriological diagnosis? Again, take diphtheria. Here we are introduced to a slight modification of the problem before us. In the case of diphtheria, as in that of

* It is true that at Berlin they have proved with success that a considerable number of these so-called species of Cunningham are only races of the cholera-spirillum—nevertheless case after case is being published in which spirilla isolated from cases of this disease do not accord in their characteristics with Koch's narrow limitations of the peculiarities of the cholera-spirillum.

suppurative disease (pyæmia) and of pneumonia, not to mention yet other examples, that we are dealing with a disease due to a microbe of usual pathogenic properties, there cannot, in a typical case, be the slightest doubt, yet it is possible very frequently to obtain from the healthy individual, either from the skin or again from the pharynx and mouth, cultures of a form morphologically and biologically undistinguishable, from the virulent microbes of the above mentioned disease.

This class of cases, it is true, is not quite so difficult to deal with as those previously mentioned, because while morphologically the saprophytic forms are undistinguishable from the pathogenic, a clear distinction can be gained by experimental inoculation. Animals will take the disease and die in the course of a few hours if inoculated with the pathogenic form, and will resist inoculation or die only after many days if inoculated with the saprophytic form, and yet it must be confessed that from a diagnostic point of view this morphological likeness does introduce the grave difficulty that in order to arrive at a sure diagnosis, experimental inoculation must be performed and the bacteriologist must sacrifice a very large number of animals. But even this experimental procedure only determines the pathogenic qualities of the isolated microbes ; it does not wholly settle the question of species. We know both by experiment and study of growths obtained from various cases that pathogenicity is a variable quantity, just as are ferment production and optimum temperature of growth.

Of course I must acknowledge that in speaking thus I am looking and making you look at one aspect of the case, but I am doing this purposely, because unless this aspect be duly contemplated, there is a danger of wholesale and uncertain diagnoses being made, and if bacteriology is to be the indispensable adjunct to departments of public health, it is urgently necessary that during the next few years, while the usefulness of bacteriology in diagnosis is under trial, the very greatest care be taken to preclude

hasty and incorrect diagnoses. I acknowledge freely, for example, that even without experimental inoculation one is generally able to determine by bacteriological methods whether a given case is or is not one of diphtheria ; where the true disease exists, there the number of colonies developing at the end of twelve to twenty hours is relatively enormous ; whereas, in a case where the bacillus present is not pathogenic the number present upon the surface of the medium is very few.

But making all acknowledgments of this nature that can be made, I still believe that what I say is worthy of earnest consideration and constant remembrance on the part of the bacteriologist. Not until some absolute method for distinguishing between various species of bacteria has been elaborated, will bacteriologists be able to make an absolute diagnosis in this most important class of doubtful and suspected cases. And for my own part I am inclined to believe that no such method will ever be devised. What I say may, to some at least, appear heretical, nevertheless it is my opinion, and I find that it is the opinion of most of the bacteriologists whom I have met that with increasing knowledge there is increasing difficulty in sharply defining the various species of bacteria. That this should be so seems to me to be only natural, for what are bacteria but the very simplest forms of life with which we are acquainted, of shape so simple that throughout the whole of the group we have but a passage from sphere to straight rodlet, to curved rodlet, to spirillum, forms without sex and multiplying in the main by fission or division.

As Weissman has remarked with regard to a similar simple form, suppose that an amœba attached to some small particle in a current gains or protects itself by a thickening of its ectoderm along the surface exposed to the current, then if that amœba divides, each of the two amœbæ will possess the same characteristic of the slightly thickened ectoderm, and remaining in the same region or under the same conditions, all the descendants of this one amœba

must inevitably possess this same characteristic, and in this way a special race of amœbæ must tend to be produced. So it is with the bacteria, slight alterations of environment must affect, and, it has been proved experimentally, undoubtedly do affect the characters of the microbes subjected to those changes, and there is an absence of that beneficial effect of sexual fusion and reproduction to preserve the mean characters of the species. Given any one form of microbe it can only retain its special characters over any long period of time by retaining a like environment, and thus it is that we must expect to find not so much sharply-defined species of pathogenic microbes, as fairly well defined groups of pathogenic microbes presenting slight divergences either in virulence or in morphological characters, or in power of fermentation or in all of these conditions, the microbe varying to a slight extent according to variations in environment. In cases of disease that are what is termed most typical there we must expect to find and to isolate the microbe most nearly presenting typical characters. In our doubtful and difficult cases we must equally expect to find microbes departing from the type. It may be that in the individual showing atypical symptoms, some peculiarity in his system, some increased or lessened power of resistance to the inroad of the bacteria, may bring about a modification of the microbe. It may be on the other hand that through unusual environment the microbes have become modified prior to their entry into the system, and thus rendered capable of producing only a modified disease. Probably both of these are factors. In either case it appears to me that the bacteriologist of the future will not so much recognize sharply-defined types as he will group together under broad headings, varieties or races of bacteria having common characters of growth and somewhat similar action upon the organism; while the officer of public health, meeting with a member of one of these groups, associated with a not perfectly typical case of disease, will treat it as suspicious, and will treat a case from which is isolated, not necessarily as one of clearly-

defined disease, but as one worthy of detention and observation ; that is to say, in the future it should not be necessary to make an absolute and possibly incorrect diagnosis, but it will be deemed justifiable to simply state that the case is suspicious, inasmuch as the bacteriological evidence is suspicious. As to this grouping of bacteria, there is already a fair consensus of opinion with regard to certain pathogenic forms ; for example, we recognize broadly a group of micrococci producing suppuration, of bacilli causing the development of tuberculosis in different animals, of spirilla inducing choleric form diarrhœa, of micro-bacilli of acute septicæmia in various genera of animals. But we still know very little about the relationship of the members of the various groups.

It has seemed to Dr. Wyatt Johnston and to myself, as well as to many other bacteriologists, that the best field for establishing the laws of grouping is to be found in a study of the innumerable slightly varying forms discoverable in ordinary water. From the very wealth of the bacterial flora in water, the subject of these bacteria in the water supply is in an absolutely chaotic state, so chaotic that now-a-days one can scarce name and describe a new species, for fear lest the slightly different characters given by some other observer in some other part of the world, as those of a species which he has isolated, be that of some variety of the same species. It has seemed to us that the only way of emerging out of this chaos is for a series of laboratories to work out each one of the group of microbes ; one laboratory, for instance, taking those producing green pigmentation ; another the red pigment bacteria ; another the *Bacillus Coli Communis* with all its varieties in contaminated water. By this means, working out a very large number of cultures isolated from regions all over the continent, the points of resemblance and of divergence of these cultures will best be determined, and as I say from the study of a large number of closely-allied forms, it will be that the laws of grouping can be determined ; in fact only

by this method can we establish some guidance to lead us out of our present difficulties. The scheme, it is true, is a large one and may possibly be found impracticable ; nevertheless we deem it worthy to make the attempt to gain the co-operation of others, and we hope that before long, with this co-operation of other laboratories throughout America, some good work may be initiated in the direction here indicated.