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THE ETIOLOGY OF MEMBRANOUS RHINITIS (RHINITIS FIBRINOSA).

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(*From the Laboratory of Hygiene, University of Pennsylvania.*)

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DURING the past year or two the condition of the nasal mucous membrane commonly known as membranous rhinitis has occasionally claimed the attention of the bacteriologist, the result of whose studies has been to show that a fair proportion of cases of this relatively rare disease are of a diphtheritic character, and that diphtheria-bacilli possessing their full virulence can often be isolated from them.

These observations, in connection with the fact that this affection is commonly looked upon as non-communicable, call for certain modifications in the care of these cases—modifications concerning less the treatment than the isolation of these patients; for, in so far as I am prepared to say, the treatment received by them is that which might be, and oft-times is, profitably employed in typical pharyngeal and laryngeal diphtheria.

But, as has been said, these cases are usually not

[1] Read before the College of Physicians, Philadelphia, May 3, 1893.

considered of a dangerous character, and are practically never isolated or prevented in any way from mingling with, and, indeed, often coming into intimate contact with healthy individuals.

They are, as a rule, seen in dispensary practice; they rarely or never present constitutional symptoms, and for these reasons they do not receive the attention that their gravity indicates. I have no positive evidence that diphtheria has ever been contracted from one of these cases, but from what we now know of them it is not improbable that this has more frequently happened than has hitherto been supposed. The comparative rarity of this disease necessarily limits the opportunity presented for its study, but the observations that have been made by reliable authorities point so directly to the diphtheritic nature of many of these cases that, when possible, it seems advisable to insist upon the bacteriological examination of all pseudo-membranous conditions of the nasal cavity that are not directly and positively traceable to other causes.

As results of such studies that have been made, Concetti,[1] in five cases of pseudo-membranous rhinitis obtained from two of them by culture-methods the virulent diphtheria-bacillus; in two others, a direct history of infection from one case to the other, with, in one of these latter cases, subsequent diphtheritic paralysis; while in the fifth case there was a secondary appearance of a membranous condition in the larynx. In all five cases the course was chronic, and, with the exception of the last case, was limited to the nose.

Stamm[2] examined, by bacteriological methods,

four cases of typical membranous rhinitis, and found in all of them the virulent bacillus diphtheriæ.

Baginsky[3] describes two cases of membranous rhinitis, both of which ran a benign course, and from both of which the bacillus diphtheriæ was obtained by culture-methods.

In his elaborate researches upon diphtheria and allied pseudo-membranous inflammations, Park[4] gives the results of analysis of six cases of the disease. In all of these cases the Klebs-Loeffler bacillus was present—in five of them in relatively large numbers. As is usually observed, these cases ran a benign course, and no history of infection was obtained from any of them.

During the past nine months we have had an opportunity of examining three cases of membranous rhinitis, in all of which the disease was limited to the nasal cavity. For the first case we are indebted to Dr. B. Alexander Randall, of this city, who saw the child in the dispensary service at the Children's Hospital, and kindly permitted us to make an examination of a portion of the membrane removed by him. The clinical history of the case is not complete, for the child disappeared, and did not return to the dispensary. The bacteriological examination of this case, which was made by Dr. Ghriskey, revealed the presence of numerous colonies of bacillus diphtheriæ which, when inoculated into guinea-pigs, caused the death of the animals with all the usual pathological lesions commonly produced by this organism in the bodies of guinea-pigs. There was no apparent diminution of viru-

lence, and no deviation in the morphology of these organisms, or in their cultural peculiarities, from those common to diphtheria-bacilli obtained from undoubted cases of primary diphtheria.

The two remaining cases are especially interesting from the fact that they occurred in two children in the same family, and doubtless represent an example of direct infection from one child to the other. For these cases I am indebted to Dr. Walter J. Freeman, of Philadelphia, who has kindly supplied me with the following histories.

The first of the two cases was a girl, M. W., aged seven years, who had had trouble with the nose for six or seven weeks prior to examination. It began as a cold; there was no headache, no fever, no sore-throat. Both nares were stopped up at the time of examination by thick membranous deposits, which were so adherent that in removing a piece, epistaxis of such a degree occurred that it became necessary to tampon the anterior portion of the nose for twenty-four hours. Ten days afterward the child appeared at the clinic; the membrane had entirely disappeared under treatment, and she was pronounced well.

Three days after this first child came to the dispensary the younger sister, aged two years, was brought by the mother, who stated that one week prior to that date the child had vomited, and on the evening of that day had a fever; was without appetite; was restless at night; the breathing was heavy and the nose "stopped up." Examination of this child in the dispensary revealed the presence of membrane in both nares. There was no sore-throat nor had there been any, and the temperature was 99°.

On April the 11th, twelve days after this child first appeared at the dispensary, I had an opportunity of making a bacteriological examination of the deposit in the nose. At this time both nares contained membrane, but not sufficient to plug them completely. The breathing of the child was principally through the mouth; there was no sore-throat, and otherwise she showed no evidence of any abnormal condition. The result of the bacteriological study of the membrane from the older sister revealed the presence of the Klebs-Loeffler bacillus in large numbers. Cultures from single colonies were not only identical in all morphological and cultural respects with those of Loeffler's bacillus as obtained from a genuine case of diphtheria, but also, like these, when inoculated subcutaneously into guinea-pigs, caused death in less than forty-eight hours, the autopsy revealing the pathological lesions characteristic of these inoculations.

From the younger sister, cultures of bacilli morphologically and biologically identical with Loeffler's bacillus were obtained, but when inoculated into guinea-pigs they were found to be of much lower degree of virulence than those obtained from the older sister. They did not cause the death of the animals, but produced only a local swelling and a very temporary indisposition, from which they recovered. In confirmation of Park's observation, the cultures obtained upon the day of examination from the older sister, and which were virulent, as stated, at that time, were found after thirty days not only devoid of virulence, but indeed devoid of vitality, and it was impossible to get them to grow again, even

under the most favorable conditions of cultivation. Except for the absence of pathogenic properties, the bacilli obtained from the latter case seen by me could not, by any of the means usually employed, be differentiated from the genuine virulent bacillus diphtheriæ. Two guinea-pigs were inoculated with relatively larger amounts of cultures from two distinct single colonies on the original tubes from the nose, but, as stated, they have not succumbed to the operation.

The absence of virulence from the cultures of the latter case is not entirely surprising in the light of Park's observations: who found that in the six cases of rhinitis examined by him, all of which ran a benign course, the bacilli obtained in culture were all of a low degree of virulence, though it is interesting, in view of the probability of infection from one sister to the other in my cases, that in the one there should have been virulent and in the other non-virulent organisms, otherwise identical. Whether this can be due to the prolonged efforts of the tissues in resisting invasion, gradually depriving the organisms of their disease-producing powers, or to the repeated application of disinfecting solutions to the surfaces upon which they are located, it is impossible to say, but certainly we know that particular pathogenic organisms, if subjected for only a relatively short time to the action of disinfectants, when not completely destroyed, show the effects of the treatment by reduction in their pathogenic activity.[5]

In neither of the latter two cases seen by me have I been able to obtain a history of any marked con-

stitutional disturbance that would lead one to suspect the presence of a grave condition.

It is very interesting, but a little confusing, to find the same organisms when located at different points giving rise to such essentially different clinical conditions as are seen when their seat of activity is the tissues of the fauces, as in diphtheria, and the tissues of the nasal cavity, as in membranous rhinitis. In the latter affection constitutional expression is the exception, and the course of the disease is usually more or less chronic, while the stages through which the typical diphtheria-patient passes are too well known to require rehearsal.

The differences in virulence that are often observed in the organisms obtained from cases of membranous rhinitis, and less frequently from diphtheritic patients, may serve, in part, at least, to explain the variations that are seen in the intensity, not only of the nasal form of the disease, but in true diphtheria as well. The bacilli present in genuine diphtheria are, with but few exceptions, highly pathogenic for certain animals, and while this is often true of membranous rhinitis, it is, nevertheless, not unusual to find organisms that are constant in morphological and cultural identity with the bacillus diphtheriæ, but which differ from this in the degree of their virulence, at times possessing this property, but in diminished intensity, and not infrequently being entirely devoid of it.

These observations undoubtedly offer another argument in support of the opinion advanced by Roux and Yersin,[6] myself,[7] and others, that the virulence of the bacillus diphtheriæ may be observed

to fluctuate in the degree of its intensity; at one time possessing this property in a high degree, at another presenting a decided attenuation, and, not infrequently, a complete absence of pathogenic power; and that the virulent bacillus diphtheriæ and so-called pseudo-diphtheritic bacillus are one and the same organism; the former being most commonly concerned in the production of a grave condition, associated with constant, or nearly constant, pathological and clinical expressions, while the tissue-changes and constitutional manifestations that present themselves as a result of the activities of the latter may vary with the degree of its disease-producing power. This hypothesis, of course, finds its most favorable application to those cases of rhinitis or other mild diphtheritic inflammations of which the clinical history would *a priori* almost exclude the probability of highly virulent organisms being concerned in their etiology.

With regard to the lack of constitutional disturbance in those cases of rhinitis running the usual benign course in which virulent diphtheria-bacilli are present, it must be borne in mind that not infrequently cases of genuine laryngeal or pharyngeal diphtheria are seen from which organisms possessing their full virulence can be isolated and from which all constitutional symptoms indicative of grave disorders are absent—a condition that, in the present state of our knowledge, we feel justified in referring to an exaggerated or unusual degree of resistance offered to the invading organisms by the tissues of the individual affected; a condition of the tissues formerly vaguely spoken of as "vital activ-

ity," but now generally recognized upon experimental evidence as a potent factor in repelling the inroads of disease-producing organisms.

That the organism that we have been accustomed to know as the pseudo-diphtheria bacillus, though incapable of destroying the life of guinea-pigs into which it has been inoculated, does, nevertheless, possess the power of causing in these animals limited localized tissue-changes, indistinguishable, save in degree, from those produced by the typical virulent bacillus, is borne out by microscopic examination of the tissues at the seat of inoculation in animals into which these non-virulent forms have been introduced, but which have not succumbed to the operation; for example, of the two guinea-pigs inoculated subcutaneously with cultures from the last case mentioned by me, neither of which succumbed, and in both of which only local tumefaction occurred, one that had gone for ten days with no apparent constitutional disturbance was killed after this date. The autopsy revealed, at the seat of inoculation, a yellowish area marked by numerous hemorrhagic points and surrounded by a very limited zone of edema not over 0.5 c.m in extent. This yellowish area was firmly adherent to the overlying skin and extended into the substance of the abdominal wall. The peritoneum beneath it was slightly reddened; the inguinal gland on the side inoculated was very slightly enlarged and reddened. Upon opening the peritoneal and pleural cavities no fluid was present; the retro-peritoneal lymph-glands were neither enlarged nor reddened. The intestines were normal; the kidneys and liver were

normal; the spleen was dark in color, otherwise normal; the adrenal bodies were small and pale, and upon section contained a brownish fluid; there was no excess of fluid in the pericardium, and the lungs were normal. The subcutaneous lymph-glands over the body, except those in the groin nearest the seat of inoculation, showed no change.

Culture-media (Loeffler's blood-serum and agar-agar) inoculated from the seat of inoculation, the blood of the heart, the liver and spleen, remained sterile.

Microscopic examination of sections of the seat of inoculation, hardened in alcohol and stained with fuchsin, revealed a condition in all essential respects identical with that described by Welch and Flexner[8] at the seat of inoculation of animals dead after the subcutaneous introduction of virulent cultures of this organism. There was the same emigration and destruction of leukocytes, the nuclei of many of which were conspicuously disintegrated. The nuclei of the fixed cells were also seen to be undergoing destruction. Many of the muscle-fibers were hyaline, and at places were seen to be penetrated by leukocytes. When stained by Weigert's fibrin-stain a delicate network of fibrin could easily be made out. In short, the tissue-changes were in all respects, save for a diminution in degree, identical with those produced by the virulent bacillus diphtheriæ.

For this reason we are inclined to the opinion that the term "pseudo-diphtheritic bacillus" as applied to an organism in all respects identical with the genuine diphtheritic bacillus, save for its in-

ability to kill guinea-pigs when inoculated subcutaneously, is a misnomer, and that it would be more nearly correct to designate this organism as the attenuated or non-virulent diphtheritic bacillus, reserving the term "pseudo-diphtheritic" for that organism or group of organisms (for there are probably several) that is enough like the diphtheria-bacillus to attract attention, but is distinguishable from it by certain morphological and cultural peculiarities aside from the question of virulence.

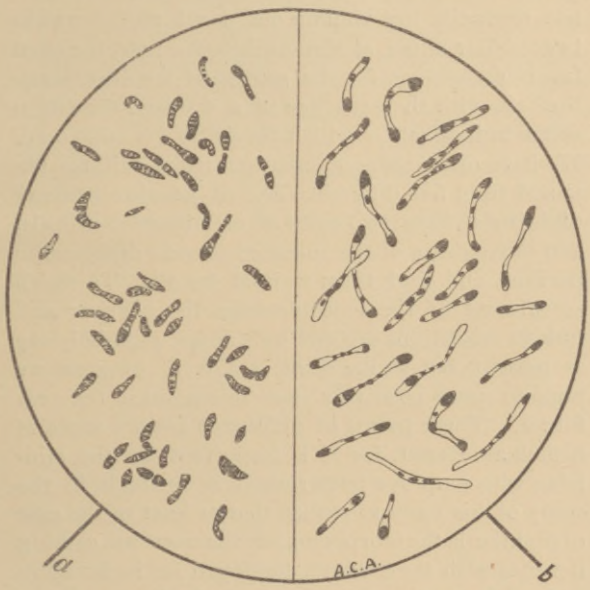
It is a well-known fact that many pathogenic organisms—conspicuous among these being the diplococcus pneumoniæ, the staphylococcus pyogenes aureus, and the group of so-called hemorrhagic septicemia organisms—undergo marked variations in the degree of their pathogenic properties; and yet these organisms, when found either devoid of this peculiarity, or possessing it to a diminished degree, are not designated as "pseudo" forms of these organisms, but simply as the organisms themselves, the virulence of which, from various causes, has been modified.

Another interesting point to which Park calls attention is the peculiar morphological variations that he observed in the organisms obtained by him from the six rhinitis cases that came under his observation. He states that the bacilli from the agar-agar cultures were small and often pointed, while those from the blood-serum and broth cultures were long and slender, with swollen ends. We have repeatedly noticed this condition not only in the cultures from the rhinitis cases, but from cases of genuine pharyngeal diphtheria as well. We have recently been

engaged in a series of experiments upon this point, and, though they are not as yet complete, the results thus far obtained are, we think, of sufficient importance to justify mention here.

The morphology of the organism while usually described as conspicuous for its irregularity, is, nevertheless, relatively constant under one and the same condition of cultivation. That is to say, the individuals comprising the growth on blood-serum (Loeffler's mixture) are very long, irregular, sometimes clubbed, sometimes pointed at ends, and are conspicuous for the irregular manner in which they take up the staining-fluid; while the growth of the same organism on glycerin agar-agar is far less voluminous, and the individuals composing it are, as a rule, short, ofttimes not over from one-sixth to one-fifth as long as the forms seen on blood-serum; they are pointed, curved, clubbed, spindle shaped, lancet-shaped, stain more uniformly and, without exception, possess transverse markings, when stained with Loeffler's blue, that give to them the appearance of being made up of very short segments. (See accompanying figure.) It is interesting to note the transition from the one form to the other when transferred from the one to the other culture-medium. We have repeatedly isolated from cases of diphtheria the diphtheritic bacillus by Loeffler's blood-serum method and continued the pure cultivation of this organism upon blood-serum through five and six generations, in all of which practically only the long, irregular, imperfectly-staining rods could be seen, but as soon as a cultivation upon glycerin agar-agar was made from

one of the generations, without a single exception, only the short segmented forms previously described would develop. Similarly, if the cultures were obtained from the throat upon glycerin agar-agar and



Bacillus diphtheriæ. *a*. After twenty-four hours' growth on 6 per cent. glycerin agar-agar, at 37° C. *b*. After twenty-four hours' growth on 6 per cent. Loeffler's blood-serum, at 37° C. Magnified in both cases about 1500 diameters.

continued through a number of generations on this medium, the transition from the short segmented to the long, irregular threads was seen within twenty-

four hours after transferring them to the blood-serum mixture.

All of these long, irregular forms have hitherto been referred to collectively as involution or degenerate conditions of this organism, but I cannot reconcile the voluminous development within twenty-four hours, as seen on blood-serum, the most favorable medium for the growth of the diphtheria-bacillus, with the existence of a diseased condition of the individuals of which the growth is composed. We have made these observation upon cultures obtained from five different cases of genuine primary diphtheria, from two cases of membranous rhinitis, and one culture of the so-called pseudo-diphtheritic bacillus, and find them to hold for all. To which constituent of the culture-media the peculiar and sudden transitions are due we cannot definitely say at present, but as the work is still in progress we hope to speak positively upon this point in the near future. These points of difference are not alone of technical interest, for it is important for the clinician who employs bacteriological methods in the study of his cases to realize that at least in the case of diphtheria the morphology of the organism causing it varies with the medium employed for its isolation and cultivation, and, unless he is familiar with the appearances presented by it under the varying conditions of environment, it is possible for error in diagnosis to arise, even though the manipulation of the case and the preparation of the cultures may have been practised with all of the precautions necessary to success.

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