ON THE LIFE-HISTORY OF THE MENINGOCOCCUS AND OF OTHER BACTERIA.

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THERE are in every science certain admitted facts which do not fit in with current teaching. The tendency of the ordinary worker is tacitly to ignore them; the current teaching satisfies his own particular needs, why therefore worry? But, as a matter of experience, it is by a study of these real or apparent exceptions to the rule that advance is most surely accomplished. This is true of bacteriology as of other sciences.

I cannot give a better instance than that of enteric fever. If in this year of grace there is any bacillus that has firmly established itself as a pathogenic agent it is the *Bacillus typhosus*. The specific reaction between the blood serum of the enteric patient and the bacillus is a commonplace of medical practice: take a culture of the bacillus that has been grown for years in the laboratory, kill it and make a vaccine, and by that vaccine our army in its hundreds of thousands has been immunized against the disease, and yet, although that stock culture, when killed, will cause immunity, when living it will not cause the disease. At least, no one so far has been successful in reproducing the symptoms and specific lesions of enteric fever in man or in any animal by the employment of a stock culture of the typhoid bacillus.

Or take another organism that has played an important part in connexion with "immunology," the bacillus of hog cholera. That is a disease which in swine sets up lesions of the bowel not unlike those of enteric in man. Constantly, in swine affected by the disease, cultures are to be obtained of the *Bacillus suispestifer*, and the blood serum of the affected animals agglutinates the bacillus. By analogy with human typhoid this bacillus ought to be regarded as the causative agent of the disease. But similarly inoculation of pure cultures of the bacillus will not reproduce the disease in pigs. What is more, when the disease is rife the bacillus may be isolated from the stools of unaffected animals. It might be argued that we deal with "carriers," though here there is the additional difficulty that vaccines do not surely confer immunity. To crown all, after the long and honourable career of the *Bacillus suispestifer*, in 1905 Dorset, Bolton, and McBryde proved beyond possibility of doubt that the suggestion of de Schweinitz in 1903 was correct, and that hog cholera is set up by a filterable virus, that if the blood serum of an affected hog be filtered through a "B" or even an "F" Chamberland filter, the filtrate will set up the disease in swine not previously affected by the disease. Note the paradox: The bacillus is constantly found in the intestines and in connexion with the intestinal lesions; it will not reproduce the disease, but this can be reproduced by an agent which will pass through filters which are impervious to forms as large as are bacilli.

This is not an isolated case; Petrie and O'Brien¹ have described an epizootic among guinea-pigs "complicated" by an intestinal bacillus which they cannot distinguish from the *B. suispestifer*; nevertheless they prove that the disease is caused by a "filter passer"; and Wolbach,² in his valuable review of the filterable viruses, notes two other diseases—namely, distemper in dogs and scarlet fever in man—in which there is a similar constant presence of definite bacteria, with satisfactory evidence of filterable viruses as the essential causative agents. The observations of the last two or three years appear to add typhus fever to this category.

How is it possible to harmonize these apparently contradictory observations? Here the paper now published by Hort and Caulfeild upon cerebro-spinal fever and the meningococcus³ is not merely suggestive, but, I am inclined to think, is the beginning of a revolution in our conception of the life-history of pathogenic bacteria; nay,

it may in years to come be regarded as one of the classics of bacteriological literature. This I know is a bold statement.

They adduce strong evidence in support of the view that cerebro-spinal fever belongs to this paradoxical group. That Weichselbaum's meningococcus is intimately associated with this disease is as well established as that *Bacillus typhosus* is pathognomonic of enteric fever. No one with any practical experience of the disease can reach any other conclusion; lumbar puncture followed by detection of the meningococci in the spinal fluid has become the one accepted means of diagnosis. It is true that the number of the meningococci found are not in direct ratio to the severity of the symptoms—that in very malignant cases they may be so sparse as not to be visible in smears, and only to afford rare cultures; nay, I am prepared to admit that cases may occur in which, neither under the microscope nor by our present cultural methods, can the meningococci be discovered. But, admitting this, it must also be admitted that in 99 per cent. of cases clinically recognized as cerebro-spinal fever sooner or later meningococci are demonstrable. And as further evidence of the relationship is the specific curative action of the serum of animals immunized against the disease. If during the first phase of the war the serums employed had little efficacy, those now in use in England and, I may add, in Ontario (by Colonel Connell) are reducing the mortality in a most striking manner.

But as Hort and Caulfeild emphasize, and I think rightly, we cannot by injecting laboratory cultures of the meningococcus reproduce the disease. Even in monkeys they failed to obtain results. We have been content to believe that Flexner has settled this point and by inoculating monkeys had fulfilled Koch's postulates, but, subjecting Flexner's statements to a careful analysis, Hort and Caulfeild show that he only obtained his results by using enormous doses, that after a relatively very short time he was unable to obtain cultures from the cerebro-spinal fluid, and that his results can only be interpreted as demonstrating, not the establishment of a true infection with continued growth and multiplication of the pathogenic organisms, but that large quantities of meningococci, introduced locally, by undergoing lysis with liberation of their toxins, can set up an irritation of the meninges—an intoxication.

To this extent, therefore, the meningococcus comes into the same category as the *B. typhosus* and the *B. suispestifer*.

But these observers make now a notable advance; they show (1) that while cultures of meningococci obtained from the cerebro-spinal fluid of patients do not reproduce the disease, that same fluid contains a filterable virus, a virus capable of passing through so fine a biscuit porcelain filter as the "Chamberland F"; (2) that unlike the meningococcus this virus inoculated into monkeys sets up an infectious process—namely, where it does not cause death within a few days it induces a fever which may continue for five weeks and more—a general disorder without localized inflammation of the meninges; and (3) they are able to cultivate this virus, obtaining, as did Rout and Nocard with the "ultra-microscopic" organism of pleuropneumonia of cattle, an evident clouding of fluid media, and after a series of passages outside the body they have been able to inoculate monkeys, induce the characteristic prolonged fever, and from animals so inoculated have regained the filterable virus.

These are very remarkable results. They open, it appears to me, a new field for research into the bacteriology of disease. It is true that these observers have not reproduced cerebro-spinal fever in the inoculated animals; they have, however, set up a definitely infectious disorder with fever, accomplishing more than is obtainable with pure cultures of the meningococcus.

Assuming these observations to be correct—and I have carefully studied the technique employed, the cultures and preparations obtained, and can detect no flaw!—the question arises, What is the meaning of this association of meningococcus and filterable virus? Previous workers with diseases belonging to this group have at most suggested a symbiosis; that the one, the filterable virus,

* A fuller report, with ampler details of the experiments, will be found in the *Journal of the Royal Army Medical Corps* for September, 1916.

¹ Save, perhaps, that a more sensitive medium of growth might have converted some of their negative results with the cerebro-spinal fluid of patients into positive; this, however, does not vitiate the main argument.

prepares the way for the growth of the bacterial species. Hort suggests, and believes that he has evidence supporting the suggestion, that filterable virus and coccus are two phases in the life-history of one organism.

Have we all these decades been wrong in our faith that bacteria are the simplest of all living forms of life, possessed of asexual multiplication by fission only? (Sporulation as exhibited by some species is, it may be noted, not a mode of multiplication, but of tiding the race over evil days.) May there not be intercalated other phases in the life-history of the schizomycetes? I remember that a quarter of a century ago Emile Roux pointed out to me that, employing every care, not a single tubercle bacillus might be detectable in the sections made from a caseous tubercle, and yet inoculate some of the caseous material into a guinea-pig, and disseminated tuberculosis results. Here is no question of spores, as generally understood. Heat the material to 80° C. for an hour, and it is rendered innocuous. If we dealt with heat-resisting spores this would not be the case. As a matter of fact, small Gram-positive granules can be seen in such caseous material, very similar to Much's granules in Hodgkin's disease, sometimes isolated, sometimes in short chains.

In 1901, if my memory serves me aright (I am away from my books), Abbott, Nicholson, and I published a paper in the *Journal of Experimental Medicine* that bears upon this point. We found in the liver and gall bladder in cases of hepatic cirrhosis minute granules, generally in pairs, sometimes in rows of three, so small that they could only be defined by the $\frac{1}{2}$ in. immersion lens. In the bile we found larger (but still small) diplococoid bodies, and making cultures of these we obtained in case after case the development of *Bacillus coli*. We entitled our paper "On the diplococoid form of the colon bacillus." Some few years later Wolff-Eisner to a large extent confirmed our findings. Looking at preparations of Hort and Caulfeild's cultures of their filterable virus the appearances reminded me vividly of my elusive minute bodies. I admit that I regarded my bodies as degenerative and due to the action of the cells and body fluids upon the organisms. But it is within the bounds of possibility that, as with many of the protozoa, some bacteria, at least, may afford an encystment stage, followed by the liberation of minute elements which in turn may grow into larger forms which now undergo asexual multiplication. This possibility must now be tested, and these, or other observers, must study other diseases and pathogenic organisms, repeating Hort's method and keeping this possibility constantly in view.

I say this knowing full well that the academic bacteriologist is apt to look with suspicion upon Dr. Hort's work, because Hort is not of his class, but a Harley Street consultant, whose heterodox but most suggestive papers of the last few years have been the outcome of laborious hours in his own laboratory, snatched from his other work. I admit that I have had the same suspicions. Just as to become an expert violinist it is proper to begin to play the fiddle in early youth, so it is almost impossible for a man who begins to be interested in bacteriology in his maturity to master the technique. He may have ideas, may devise admirable apparatus and modes of approaching his problems, but he lacks and must lack manipulative dexterity. The course which seemed to me best calculated to remove this danger and to determine the truth was for Dr. Hort to associate with himself an independent technician of proved ability. This Dr. Hort did when he asked the D.M.S. Canadians to attach Captain Caulfeild to Addington Park for this special investigation, under the auspices of the surgeon-generals of both navy and army, Captain Caulfeild having been Demonstrator in Pathology of Toronto University, later Assistant in Experimental Medicine under the Chair of Medicine in the same university, and having published valuable work upon immunity and the tuberculin reaction in tuberculosis. The work thus demands and must receive consideration. After all it is the peculiar glory of British science that so many of its greatest triumphs have been achieved outside the schools by Priestleys, Daltons, and Darwins, and other educated amateurs.

REFERENCES.

¹ *Journal of Hygiene*, 1910; vol. x. ² *Boston Med. and Surg. Journal*, 67, 1912, p. 419.

Reviews.

THE UMBILICUS.

DR. CULLEN has added one more standard volume, the *Embryology, Anatomy, and Diseases of the Umbilicus*,¹ to the series of publications issued by the Johns Hopkins School of Medicine. It contains full quotations of the records of other observers and reports of cases occurring in the experience of the author and his colleagues. The illustrations are of high merit. Mr. Horn, whose brilliant work is so familiar to all who study the works of Drs. Kelly and Cullen, unfortunately died before he could prepare some of the earliest drawings, but Dr. Cullen has secured the services of Mr. Max Brödel, Director of the Department of Arts as Applied to Medicine in the Johns Hopkins Medical School, and rightly awards to that artist the credit of playing the principal part in investigations throwing light on the development of the umbilicus in the embryo, and on its variations in the adult; demonstrated by sixty sketches taken from patients in the wards of the Johns Hopkins Hospital. Attention may be particularly directed to an excellent drawing, representing a dissection of the umbilical region of the adult viewed from within, and to others of umbilical hernia associated with pendulous abdomen, and the stages of the radical operation for its cure. Dr. Cullen's chapters on umbilical hernia, umbilical infections, and Meckel's diverticulum and the complications to which it may give rise, will be studied with interest by surgeons. The author informs us in his preface that his book is founded on researches commenced twelve years ago in association with a case of cancer of the navel under his personal observation, and the part of the book dealing with tumours is very good. He followed up numerous after-histories, corresponding in some cases with observers in this country. He also communicated freely with English writers when engaged on his numerous chapters on the urachus, a subject about which much has been written during the past thirty years by British gynaecologists. Dr. Cullen has quite rightly saved from oblivion Wutz's monograph on urachal cysts, published in *Virchow's Archiv* in 1883, and he has shown much discretion as to the acceptance of reports of large non-infected urachal cysts. The pathology and treatment of patent urachus is discussed at length, and Dr. Cullen has very prudently quoted Dr. Edward III's warning, which is most important for the general surgeon to remember whenever he chances to come across this condition. Should the lower part of the urachus be uninvolved at the time of the operation, being reduced to an apparently impervious cord, it is not safe to treat it by ligature, as there is often a minute canal lined with epithelium in the cord; the ligature may not destroy the epithelium, and so the canal may open up from below after a time and a bad urinary fistula will be the result, an accident already recorded in the history of surgery.

NOTES ON BOOKS.

DR. GANT'S book on the various diseases of the gastro-intestinal tract² is a highly meritorious compilation, based on the extensive literature of the subject and the author's own experience. There is very little in it about diseases of the stomach; the title-page refers to the gastro-intestinal tract, the title on the book's back mentions intestinal diseases only, and the text is concerned almost entirely with the one subject of diarrhoea. The author goes in strongly for classification and subdivision, far more strongly than practical experience would justify; thus his "etiologic classification of diarrheas" on pp. 22 and 23 contains something like 150 classes and varieties of diarrhoea. Many of the illustrations are excellent, though not a few have suffered from too enthusiastic retouching. There is a great deal of useful information in the book, but it is often presented in unattractive forms and buried beneath a mass of verbiage. Compressed to half its

¹ *Embryology, Anatomy, and Diseases of the Umbilicus, together with Diseases of the Urachus*. By Thomas Stephen Cullen, Associate Professor of Gynaecology in the Johns Hopkins University. Philadelphia and London: W. B. Saunders Company, 1916. (Sup. roy. 8vo, pp. 690; 7 plates, and 269 figures. 35s. net.)

² *Diarrheal, Inflammatory, Obstructive, and Parasitic Diseases of the Gastro-Intestinal Tract*. By S. G. Gant, M.D., LL.D. Philadelphia and London: W. B. Saunders Co. 1915. (Roy. 8vo, pp. 604; 181 figures. 25s. net.)