REMARKS
ON
MICRO-ORGANISMS: THEIR RELATION TO DISEASE.*

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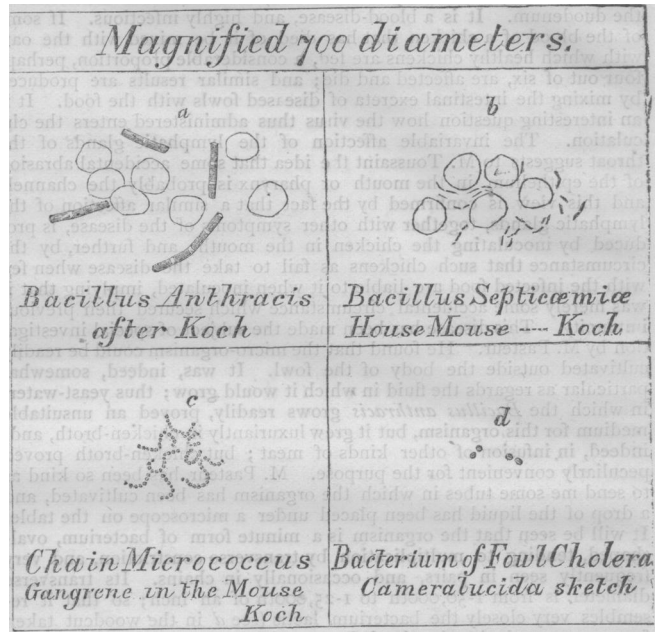
THE relation of micro-organisms to disease is a subject of vast extent and importance. If we compare the present state of knowledge regarding it with that of twenty years ago, we are astonished at the progress which has been made in the interval. At that time, bacteria were little more than scientific curiosities: whether they were animal or vegetable, few people knew or cared; but most regarded them as animals on account of the active movements which they often exhibited. That they were causes of putrefaction, or other fermentative changes, was a thing not thought of; and the notion that they had special relations to disease would have been regarded as the wildest of speculations. Now, however, a mass of information has been accumulated regarding all these points, of which it would be hopeless for me to attempt to give even a brief sketch in the time at my disposal; and all that I can do is to present to the Pathological Section a few examples illustrating the progress which is being made in this department of research.

First, I will mention some examples of the labours of Dr. Koch, of Wollstein, in Germany. Though a hard-worked general practitioner, Koch has continued to devote an immense amount of time and energy to his investigations: and by a combination of well-planned experiments, ingenious methods of staining bacteria out of proportion to the tissues among which they lie, a beautiful adaptation of optical principles to render the coloured object discernible by the human eye, and, further, by a most successful application of micro-photography, he has succeeded in demonstrating the presence of these minute organisms in a manner never before attained.

The *Bacillus anthracis* is now universally recognised among pathologists as the cause of splenic fever, so fatal among cattle in this and other countries, and capable of being communicated to various other animals, and, among the rest, to the human species, as has been lately illustrated by the so-called woolsorters' disease, in the North of England. The *Bacillus anthracis* is a large form of bacterium, as is shown at *a* in the accompanying woodcut. It is there shown along with red blood-corpuscles of a mouse, and the rods of which it is composed are seen to be in diameter nearly one-fourth of that of the red corpuscles. Koch's method of staining the sections shows in the most beautiful manner that these bacilli are not only present in the spleen and some other organs, but that they people the blood in the minute vessels of all parts. Koch has thus added to our conviction that the bacillus is the cause of the symptoms, seeing that, as he remarks, it is impossible to suppose that an organism can develope in such enormous numbers at the expense of the vital fluid, without exerting a serious influence upon the system.

But the most striking and important results of Koch's method of investigation are those which relate to organisms of much smaller dimensions. He found that, if putrid liquid is injected under the skin of a mouse, the animal may die in the course of a short time, as the result of the chemically toxic effects of the products of putrefaction absorbed into the circulation; but, if it survive this primary disorder, it may succumb in the course of about two days to blood-disease. If the point of a lancet be dipped into the blood of the heart of a mouse which has died in this way, and a scratch be made in the skin of a healthy mouse with the envenomed instrument, the second mouse dies with similar symptoms to those of the first, the poison being absolutely certain in its virulent operation; and the same thing may be continued indefinitely through any series of animals. If now sections be made, and stained, and examined by Koch's procedures, it is found that the entire blood of the diseased animal is peopled with bacteria, resembling those of the *Bacillus anthracis* in the enormous multitudes in which they are produced, and also in their rod-like form, but differing from them in being exquisitely minute and delicate, as is shown at *b*, drawn on the same scale as *a*, where it is seen that the diameter can only be represented by a slender streak not one-eighth of the diameter of the *Bacillus anthracis*, and such as, before the introduction of Koch's method, would have escaped notice altogether. Now, this disease is totally distinct from pyæmia, being not accompanied with multiple abscesses or embolism; and thus it has been shown by Koch that septicæmia may exist as a deadly blood-disease, caused by the development of micro-organisms, being equally distinct from pyæmia and from the chemically toxic effects of septic products.



On some occasions, as the result of the introduction of putrid fluid under the mouse's skin, Koch found, besides septicæmia, a local affection of the seat of inoculation, in the form of spreading gangrene; and, on investigating the part, he discovered in it, exactly corresponding with the extent of the local affection, another organism very differently formed from that of the septicæmia—viz., a micrococcus, consisting of minute spherical granules arranged in linear series, like strings of exquisitely minute beads, as represented at *c* in the woodcut. Believing that this locally developing organism must be the cause of the gangrene, he tried to separate it from the bacillus of the septicæmia, and succeeded through an accidental observation of great interest. Having till that time employed the house-mouse in his experiments, he happened to try the inoculation of a field-mouse. This animal, though so closely allied, proved not susceptible of the septicæmia. The bacillus of that disease was unable to grow in the blood of the field-mouse, but the micrococcus of the gangrene could develope among its tissues. The new organism was thus obtained in an isolated form, and, when now inoculated into the house-mouse, produced in that animal gangrene pure and simple, extending for an indefinite period among its tissues.

Thus the animal body, which had previously been an obscure field of labour in this department, in which the pathologists did little more than grope in the dark, was converted by Koch into a pure cultivating apparatus, in which the growth and effects of the micro-organisms of various infective diseases could be studied with the utmost simplicity and precision.

One more example I must take from Koch's work. On one occasion, as the result of inoculating putrid liquid into a rabbit, he observed a spreading inflammation having all the clinical character of erysipelas; and, on examining stained sections of the part, he discovered another exquisitely delicate bacillus resembling the micrococcus of the gangrene, in being local in its development, while its exact correspondence in extent with that of the disease led fairly to the conclusion that it constituted the *materies morbi*.*

I will next refer to a disease occasioned by a micro-organism discovered by the eminent pathologist Professor Toussaint of Toulouse,

* Address delivered before the Pathological Section in opening a discussion on the subject at the Annual Meeting of the British Medical Association in Cambridge, August 12th, 1880.

* See *Untersuchungen über die Aetiologie der Wundinfectionskrankheiten*. von Dr. Robert Koch. Leipzig: 1878. A translation is about to be issued by the Sydenham Society.

whom I am proud to see present in this Section to-day. This disease has been somewhat inappropriately termed *Cholera des poules*, or fowl-cholera, for it is not attended with diarrhœa or any other of the symptoms of cholera; but, as it happened to be extremely destructive among the poultry-yards of Paris at the same time that an epidemic of cholera was raging in the city, the disorder that prevailed among the fowls was also given the name of cholera. The lesions by which it is chiefly characterised are great swelling of the chains of lymphatic glands in the vicinity of the trachea, pericarditis accompanied with great effusion, and congestion, and it may be ulceration, of the mucous membrane of the duodenum. It is a blood-disease, and highly infectious. If some of the blood of a chicken that has died of it be mixed with the oats with which healthy chickens are fed, a considerable proportion, perhaps four out of six, are affected and die; and similar results are produced by mixing the intestinal excreta of diseased fowls with the food. It is an interesting question how the virus thus administered enters the circulation. The invariable affection of the lymphatic glands of the throat suggests to M. Toussaint the idea that some accidental abrasion of the epithelium in the mouth or pharynx is probably the channel; and this view is confirmed by the fact that a similar affection of the lymphatic glands, together with other symptoms of the disease, is produced by inoculating the chicken in the mouth; and further, by the circumstance that such chickens as fail to take the disease when fed with the infected food are liable to it when inoculated, implying that it was merely some accidental circumstance which secured their previous immunity. This disease has been made the subject of special investigation by M. Pasteur. He found that the micro-organism could be readily cultivated outside the body of the fowl. It was, indeed, somewhat particular as regards the fluid in which it would grow; thus yeast-water, in which the *Bacillus anthracis* grows readily, proved an unsuitable medium for this organism, but it grew luxuriantly in chicken-broth, and, indeed, in infusion of other kinds of meat; but chicken-broth proved peculiarly convenient for the purpose. M. Pasteur has been so kind as to send me some tubes in which the organism has been cultivated, and a drop of the liquid has been placed under a microscope on the table. It will be seen that the organism is a minute form of bacterium, oval-shaped, tending to multiplication by transverse constriction, and very frequently seen in pairs, and occasionally in chains. Its transverse diameter is from 1-50,000th to 1-25,000th of an inch; so that it resembles very closely the bacterium lactis (see *d* in the woodcut taken from a *camera lucida* sketch of the organism sent by M. Pasteur). So far as I am aware, this is the first time this bacterium has been shown in this country. Now, it was found by Pasteur that the organism could be produced in chicken-broth in any number of successive cultivations, and to the last retain its full virulence; so that, if a healthy chicken were inoculated with it, the fatal disease was produced as surely as by inoculation with the blood of a fowl that had died of the complaint. This was pretty conclusive evidence that the organism was the cause of the disease, and that it constituted the true infective element; because any other material that might be supposed to accompany it in the blood of the diseased animal must have been got rid of by the successive cultivations in chicken-broth.

The growth of the organism occasions no putrefaction in the liquid, so that this is a good example of a bacterium which is most destructive as a disease, but which is at the same time entirely destitute of septic property, in the primitive sense of that term as equivalent to putrefactive. After the bacterium has grown for a certain time in a given portion of chicken-broth, it ceases to develop further; and when this is the case, although the broth has lost only a very small proportion of its substance by weight, and although, as aforesaid, it has not undergone putrefaction, and still constitutes an excellent pabulum for ordinary forms of bacteria, the bacterium of the fowl-cholera, though introduced from some new source, is incapable of growing in it. This fact certainly seems highly suggestive of an analogy with the effects of vaccination, or those of an attack of measles or scarlatina in securing immunity from the disease for the future. Here we have a certain medium invaded by a virus capable of self-multiplication, as is the case with those diseases in the animal body; the medium itself little affected chemically by the growth of the virus within it, nevertheless rendered unfit for the development of that virus for the future. But something more than the suggestion of analogy with vaccination has been effected by M. Pasteur. By cultivating this bacterium in a particular manner, which he has not yet published, he enfeebles the organism, as he believes, and produces such an alteration in it that, when inoculated into a healthy fowl, it produces only a modified and no longer fatal form of complaint, but the bird is thereby rendered secure against taking the ordinary form of the disease. It has been really vaccinated, if we adopt M. Pasteur's extension of the term vaccination to other similar cases; for just as we speak of an iron milestone, we may, if we please, apply the term vaccination to the use of a virus other than the vaccine obtained from a heifer. But though the vaccination with the modified bacteria and the fowl-cholera does not occasion the fatal disease, it produces pretty severe local effects. If inoculated on the breast of the fowl, it causes a limited gangrene of the pectoral muscle, the affected part falling off in due time as a dry slough. Through the great kindness of M. Pasteur, I have now the opportunity of showing to the Section a hen which has been treated in this way. You observe a slough on the breast of the bird, about as large as a penny piece; it is dry, and obviously old. The fowl has been some days in my possession subsequently to its journey from Paris; but though more than enough time has elapsed since the inoculation to have caused its death, had the disease been in the ordinary form, it is, you see, in good health, bright and active, and it both eats and sleeps well.*

I will now return to the *Bacillus anthracis*, with regard to which I shall have again to refer to the labours of M. Toussaint. First, however, I must allude to the work of some of my own countrymen. In March 1878, an experiment was made at the Brown Institution, at the suggestion of Dr. Burdon Sanderson, of inoculating a calf with the blood of a guinea-pig which had died of splenic fever, which is exceedingly fatal to rodentia. The result was that the calf took the disease, but in a mild form, and recovered from it; and a similar fact was observed in two heifers treated in the same way.†

This line of inquiry has since been followed up by Dr. Sanderson's successor at the Brown Institution, Dr. Greenfield, with the view of ascertaining whether the milder form of the disease in cattle, resulting from inoculation with the blood of rodentia affected with it, confers upon the cattle immunity from the complaint in its fatal form; or, to use again M. Pasteur's expression, whether the cattle have been vaccinated with reference to anthrax. And I have great pleasure in being able to inform the Section, by Dr. Greenfield's permission, that the question has been answered in the affirmative; and that one bovine animal, inoculated seven months ago with virus from a rodent, has proved itself, on repeated inoculations, entirely incapable of contracting splenic fever, remaining free from either constitutional or local manifestations of it.

And now to return to M. Toussaint, who has made observations with regard to this same subject of vaccination against anthrax fraught with the very deepest interest. The question arises, with regard to effective vaccination, using the term in Pasteur's general sense: Is it essential that micro-organisms should develop in the blood of the animal in which immunity from further attacks of the disease is to be secured? or is it possible that the necessary influence upon the system may be exerted by merely chemical products of the growth of that organism in some other medium? With the view of approaching the solution of this question, M. Toussaint has performed experiments of injecting into the blood of healthy sheep blood taken from an animal affected with splenic fever, but deprived of the *Bacillus anthracis*. Taking blood from a sheep just on the point of death, when the bacillus has presumably produced all its possible effect upon the vital fluid, M. Toussaint proceeds to deprive it of the living bacillus in either of two ways—by filtration, or by destroying the vitality of the organism. The former he effects by mixing the blood with three or four parts of water, and then passing it through about twelve layers of ordinary filter-paper. The bacillus, in consequence of its large dimensions, is entirely retained by this form of filter, as is proved by the fact that the filtrate no longer gives rise to the organism in a cultivating liquid or in a living animal. Nevertheless, if injected in considerable quantity into the circulation of a healthy sheep, it produces a true vaccinating influence; that is to say, secures immunity from splenic fever. But, what is further extremely interesting, in order that this change in the constitution of the sheep may be brought about, the lapse of a certain time is essential. If a vaccinated sheep be inoculated with anthrax within a few days of the operation, it will die of splenic fever; but if from twelve to fifteen days be allowed to elapse, complete immunity is found to have been produced. Similar results followed from the injection of anthrax blood treated by M. Toussaint's other method, which consists of maintaining it for a considerable time at a temperature of 55° Cent. (131° Fahr.), which has the effect of killing the bacillus; after which half per cent. of carbolic acid is added, to prevent putrefaction of the liquid. The blood treated in this way having been proved to be free from living bacilli by negative results of an experiment upon a rodent, about four cubic *centimètres* are injected into the venous system of a sheep, with the effect of producing the same protective influence against splenic fever as is ensured by the filtered blood. These experiments are still in pro-

* M. Pasteur's researches on this subject are related in the *Comptes Rendus de l'Académie de Science*, February, April, and May, 1880.

† See Report on Experiments on Anthrax by Dr. Sanderson (*Journal of the Royal Agricultural Society of England*, vol. xvi, s.s., part 1.

gress; but M. Toussaint informs me that he has already ascertained the existence of immunity against anthrax for three months and a half in both sheep and dogs treated in this way.

I need hardly remark on the surpassing importance of researches such as these. No one can say but that, if the British Medical Association should meet at Cambridge again ten years hence, some one may be able to record the discovery of the appropriate vaccine for measles, scarlet fever, and other acute specific diseases in the human subject. But even should nothing more be effected than what seems to be already on the point of attainment, the means of securing poultry from death by fowl-cholera, and cattle from the terribly destructive splenic fever, it must be admitted that we have an instance of a most valuable result from the much-reviled vivisection.

I have yet one more example to give of researches in this domain of pathology; and this also has reference to the *Bacillus anthracis*. The investigator in this instance is Dr. Buchner, assistant physician in Munich. It is well known that the bacillus anthracis is morphologically identical with an organism frequently met with in infusion of hay, which may be termed hay-bacillus. Such being the case, it occurred to Dr. Buchner that they might be merely one and the same organism modified by circumstances. For my own part, I am quite prepared to hear of such modifying influence being exerted upon bacteria, having made the observation several years ago that, when the *bacterium lactis* had been cultivated for some time in unboiled urine, it proved but a feeble lactic ferment when introduced again into milk. Its power of producing the lactic fermentation had been impaired by residence in the new medium. In the case before us, indeed, the physiological difference between the two organisms seems, at first sight, so great, as to forbid the idea of anything other than a specific difference. The bacillus anthracis refuses to grow in hay-infusion in which the hay-bacillus thrives with the utmost luxuriance; and conversely, the hay-bacillus is utterly incapable of growing in the blood of a living animal, whether introduced in small or in large quantities. The hay-bacillus is remarkable for its power of resistance to high temperatures, which is not the case with the bacillus anthracis. The latter is destroyed by a very slight acidity of the liquid of cultivation, or by any considerable degree of alkalinity, whereas the former survives under such conditions. Both will grow in diluted extract of meat, but their mode of growth differs greatly. The hay-bacillus multiplies rapidly, and forms a dry and wrinkled skin upon the surface, while the bacillus anthracis produces a delicate cloud at the bottom of the vessel, increasing slowly. Nothing daunted by these apparent essential differences, Dr. Buchner has laboured with indomitable perseverance by means of experiments carried on in Professor Nägeli's laboratory, to solve the double problem of changing the bacillus anthracis into hay-bacillus, and the converse. Having devised an ingenious apparatus by which a large reservoir of pure cultivating liquid was placed in communication with a cultivating vessel, so that any cultivation could be drawn off by simply turning a stop-cock, and further cultivating liquid supplied to the organisms remaining in the vessel by a mere inclination of the apparatus, Buchner proceeded to cultivate the isolated bacillus anthracis in extract of meat for several hundred successive generations. As an early result of these experiments, he found that the bacillus lost its power of producing disease in an animal inoculated with it. Up to this point he is confirmed by Dr. Greenfield, who has found that, when the bacillus anthracis is cultivated in aqueous humour, after about six generations it loses its infective property. Then as Buchner's experiments proceeded, the appearance of the growing organism was found to undergo gradual modification. Instead of the cloud at the bottom of the vessel, a scum began to make its appearance—at first greasy-looking and easily broken up—constituting, so far as appearances went, an intermediate form between the two organisms; and in course of time the scum became dryer and firmer, and at length the modified bacillus anthracis was found to be capable of growing in an acid hay infusion, and to present in every respect the characters of the hay-bacillus. The converse feat of changing the hay-bacillus into the bacillus anthracis proved very much more difficult. A great number of ingenious devices were adopted by Buchner, who was, nevertheless, continually baffled, till at last he attained success in the following manner. Having obtained the blood of a healthy animal under antiseptic precautions, and defibrinated it also antiseptically, and having arranged his apparatus so that the pure defibrinated blood, which was to be the cultivating medium, should be kept in constant movement, so as to continually break up the scum, and also keep the red corpuscles in perpetual motion so as to convey oxygen to all parts of the liquid—in this way imitating, to a certain extent, the conditions of growth of the bacillus anthracis outside the animal body, within which the hay-bacillus could not be got by any means to develope—he proceeded to cultivate through numerous successive generations. A transitional form soon made its appearance; but the change advanced only to a limited degree, so that further progress by this method became hopeless. The modified form hitherto obtained failed entirely to grow when injected into the blood of an animal. On the contrary, it was in a short time completely eliminated from the system, just like the ordinary hay-bacillus. It had, however, been observed by Buchner that spores had never been formed by the bacillus growing in the defibrinated blood; and it occurred to him that, perhaps, if it were transferred to extract of meat, and induced to form spores there, the modified organism might yet grow in the blood of a living animal. The carrying out of this idea was crowned with success; and, both in the mouse and in the rabbit, Buchner succeeded by injecting various different quantities containing the organism in different animals. When large quantities were introduced, the animals died rapidly from the merely chemical toxic effects of the injected liquid; but, in some instances, after the period for these primary effects had passed, a fatal disease supervened—attended, as in anthrax, with great swelling of the spleen, the blood of which was found peopled as in that affection with newly formed bacilli; and the spleens affected in this way were found to communicate anthrax to healthy animals, just like those of animals which had died of ordinary splenic fever.*

Supposing these results to be trustworthy, and the record of them bears all the stamp of authenticity, I need scarcely point out to a meeting like the present their transcendent importance as bearing upon the origin of infective diseases, and their modifications as exhibited in epidemics.

I trust that these examples may suffice to convey some idea of the work now going on with reference to the relations of micro-organisms to disease.

ON THE REMOVAL OF UTERINE TUMOURS BY ABDOMINAL SECTION.†

By T. SPENCER WELLS,

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I WISH particularly to limit this discussion precisely to the consideration of the subject of removal of uterine tumours—myoma, fibro-myoma, or fibroma—by abdominal section. Such a tumour as that on the table, which was removed by Mr. Sherburn of Hull from the uterine cavity and vagina, and the removal of fibroid polypi, or the enucleation of ingrowths which project towards the uterine cavity, are beyond the scope of discussion to-day. And so is excision of the entire uterus for cancer, by Freund's method or any other; and the operation of Porro, so interesting to the obstetrician, where, in addition to the Cæsarean section, the uterus itself is excised after withdrawing the child. All these subjects are well worthy of separate discussion; and I hope they will be carefully criticised as soon as a sufficient number of facts, carefully observed and faithfully recorded, have been collected to form a groundwork for the formation of sound opinion. My object to-day is to obtain from members present any such additions to our knowledge as may assist in the formation of professional opinion upon the removal of fibroid outgrowths from the uterus towards the peritoneal cavity, subperitoneal outgrowths with a more or less perfect pedicle, or fibroid enlargements of the fundus, which may be removed with some part of the uterus itself, and with or without one or both ovaries at the same time, by such a division of the abdominal wall as is made in ovariotomy, but necessarily longer when the tumours are both large and solid. And, as I understand opening a discussion to differ from reading a paper, in so far that in the former case one hopes to elicit information from others, while in the latter we endeavour to relate what we have ourselves observed or thought, I shall now only sketch so much of my own doings and reflections as may induce others to narrate theirs, and thus assist in the removal of the doubts and difficulties which necessarily obscure any comparatively new subject at its rise and during its early progress.

In the Hunterian Lectures at the College of Surgeons which I delivered in June 1878, and which were fully reported in your JOURNAL, I reported all my cases of removal, or attempted removal, of uterine tumours through the abdominal wall; and arranged them in two tables, one containing all the necessary details of twenty-four cases where uterine tumours were removed, with or without one or both ovaries; and twenty-one cases where only an exploratory incision was made, or where, in addition, the tumour was either simply punctured or partially

* See *Ueber die experimentelle Erzeugung des Milzbrandcontagiums aus den Hemitzen*, von Haus Büchner. München, 1880.

† Address delivered in the Section of Obstetric Medicine, in introducing a discussion on the subject, at the Annual Meeting of the British Medical Association in Cambridge, August 13th, 1880. See page 373.