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LECTURES ON THE INFECTIVE PROCESSES OF DISEASE.

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LECTURE II (*continued*).—*Etiology of Septicæmia.*

WE have seen that it is easy to prepare from putrid infusion of muscle an extract which, while perfectly soluble in water, possesses the toxic property of the original material in such intensity that a very small dose of it (less than half a grain), if infused into the blood-stream of a dog, is sufficient to produce fatal septicæmic effects. We have also seen that there is good reason for thinking that these effects are entirely independent of the direct action of septic organisms, inasmuch as they are not attended with the development of such organisms in the body of the poisoned animal. If we were to limit our view exclusively to such considerations as these, we should be not unlikely to swing round to a way of thinking which might be defined as the very opposite of the germ-theory, and to express ourselves in this way: "You see, after all, that these gentlemen who have been talking about germs, Pasteur, Tyndall, Roberts, Lister, etc., are all under a delusion. These supposed organisms, whatever may be their nature, whether aerial or aquatic in their habits, whether actual or hypothetical, have nothing to do with septicæmia, and, by inference, nothing to do with disease."

To meet this tendency, I will ask your attention to the evidence by which we may assure ourselves that, although bacteria are not the agents in septic infection, they are, nevertheless, the producers of the septic poison, and that the mistake, if any mistake have been committed, consists in this: not in stating that bacteria are of pathological importance, but in asserting that because A produces B and B produces C, therefore, C cannot be produced unless A is present. It would, I think, be erroneous to say that the yeast-plant is the agent in the production of the evils of intemperance, and it is a mistake to say that bacteria are the agents in the production of septicæmia; but just as, if there were no yeast-plant there would be no drunkenness, so, if there were no bacteria there would be no septicæmia. I have now to bring before you the evidence that this is so.

As I stated yesterday, all the earlier experiments on septic infection were made with putrid infusions of the tissues of animals or plants. As all such liquids must necessarily contain proteid material, it was thought that the specific virulence must attach to some particular chemical product of the putrefactive disintegration of albuminous compounds. It was, therefore, suggested by Virchow that the proper way of searching for the septic virus was first to determine what these products were, and then to test each of them by physiological experiment. But this method is much more easily proposed than carried out, for chemists are not as yet in a position to give us very exact information as to the nature of these products. What we find in animal putrid infusions when we examine them is this. If we slightly acidulate the liquid and boil it, we find that it contains common albumin. In the uncoagulated liquid, we throw down a further quantity of proteid material by the addition of alcohol—this being in the state of peptone. The unprecipitated liquid, partly aqueous and partly alcoholic, contains two well-known bodies, leucin and tyrosin, the presence of both of which may be readily recognised by their several characters. In addition to these, various volatile products of definite chemical constitution

are present, one of which, the body indol,* distinguished by its peculiar odour recalling that of fæces, can be prepared in larger quantity and with greater facility by the action of septic bacteria on albumin than in any other way. All of the bodies I have mentioned, peptones, leucin and tyrosin, indol, and the rest, are known to occur in the small intestine as products of the action of the pancreatic ferment, so that there is a very striking resemblance between the action of the pancreatic ferment and putrefaction. The resemblance, however, by no means implies identity; for, although bacteria are always present, and must, therefore, in actual digestion, mix their fermentative influence with that of the proper digestive ferment, it has been proved by the most careful experiment, that, so far as relates to the conversion of the proteids of food into the soluble and diffusible peptones, the process of pancreatic digestion can begin and be completed without them. The ultimate products, however, are not precisely the same when bacteria are excluded, the most characteristic difference being that the volatile products I have mentioned, and particularly indol, do not appear when albumin or fibrin is subjected to the digestive action of the pancreatic ferment under conditions which either exclude the septic organisms or inhibit their development.†

So far as our present knowledge reaches, none of the known chemical products of the putrefactive disintegration of albuminous compounds can be indicated as the cause of the toxic action of putrid infusions; for in respect to each of them we have experimental evidence that, when separately introduced into the organism, in such quantity as would correspond to a poisonous dose of the septic liquid of which it is a constituent, it produces no toxic effect whatever. The inference is, therefore, suggested that the poison is not any product of the septic disintegration of proteid bodies, but a something which is much more intimately associated than any of them are with the existence and growth of the ferment-organisms themselves.

This inference has been fully justified by experiment. It has been shown by Professor Bergmann that the septic poison can be produced by the action of bacteria on material which contains no albuminous compound. He found—and we are now familiar with the fact by repeated experiments—that, if you grow bacteria in the cultivating liquid to which I previously referred, of which the composition is given in the table,‡ the first crops of bacteria are inert; but eventually you obtain a product which possesses all the virulence of putrescent animal or vegetable infusions, notwithstanding that the original liquid contained only sugar, ammoniac tartrate, and certain inorganic salts.

Let us endeavour to realise what happens. We have, to begin with, virtually a solution of ammoniac tartrate; for it can be shown that it is all that is wanted at the outset. Into that solution you introduce at one side, say a bit of glass which has not been calcined and of which the surface is consequently contaminated, *i. e.*, beset with germinative particles. The vegetation takes its start from the surface of the glass. One after another bacteria emerge into existence and visibility, and multiply with a rapidity which you can easily calculate, on the datum that each becomes two within about an hour after its birth.

Having our bacterium, how does it manufacture its virus? In order to obtain an answer to this question, I will ask your attention to the following experimental results, which, irrespectively of their bearing on the present question, are of value for the additional evidence they afford of the fundamental proposition of this lecture, *viz.*, that septicæmia is not due to the direct action of living bacteria on the blood and tissues.

* Indol (C_8H_7N) is a crystallisable body, obtained by the reduction of certain derivatives of indigo, which fuses at 52 deg. C., and is volatile at ordinary temperatures. It has no toxic properties; but its solution in water, when injected into the circulation, gives rise to the appearance of indican in the urine in corresponding quantity. See M. Jaffe, Ueber den Ursprung des Indicans im Harn; *Centralblatt für die Medicin. Wissenschaften*, 1872, p. 2; and Koukol-Jasnopolsky, Ueber die Bildung von Indol, *u. s. w.*; *Plüger's Archiv*, vol. xii, p. 78.

† Nencki, Ueber die Zersetzung der Gelatine und des Eiweisses. Bern, 1876, p. 31.—Kühne, Erfahrungen und Bemerkungen über Enzyme und Fermente, *Untersuch. des Physiol. Institutes der Universität Heidelberg*, vol. i, part iii, p. 13, of the reprint. Kühne has lately found that, when an artificial pancreatic digestion of albumin or fibrin is conducted with the addition of thymol, no indol is formed, although the process is not otherwise interfered with.

‡ The cultivation liquid contains, in 100 cubic centimetres, 30 grammes of cane-sugar, 1 gramme of ammoniac tartrate, and 0.5 gramme of potassic phosphate.

Some years ago, Dr. Hiller,* one of the most energetic and able of the opponents of the germ theory, made an experiment which has been the subject of much discussion. Having succeeded in collecting a considerable mass of bacterial material, that is, of bacteria obtained from various fluids in advanced putrefaction, on a filter, he washed the mass, just as one washes a precipitate, a great number of times; then diffused the material which had been so washed in distilled water, and injected it in repeated doses into the circulating blood of animals. The injections were entirely without effect. Hiller next proceeded to inoculate himself with the same material, and again without effect. The advocates of bacteria at once objected to Hiller's experiment, that the bacteria, not being accustomed to distilled water, were so injured by the repeated washings that they had lost their activity. The criticism, however, might just as well have been spared; for it afforded Hiller the opportunity of proving by experiment, which was of course easy enough, that the washed bacteria were as lively and as capable of development as ever.

But there is another way in which inactive bacterial liquids can be prepared: a way to which I have already adverted. In any cultivation of bacteria in a nutrient solution, the first crop (if I may use the expression) is always inert. It is not until the bacteria have gone on for many days dividing and dividing, that they begin to develop their poisonous properties, at all events, in appreciable quantity. This can scarcely mean anything else than that the mode of vegetation changes; viz., that the bacteria first formed have their place taken by others of which the form and the physiological endowments are different. Every one who is familiar with the growth of bacteria in cultivating liquids knows that there is a marked difference in appearance between the first and the subsequent growths, the former consisting mostly of rods (bacteria proper), which appear early, the latter of spheroids or micrococci. They differ not only in form, but also in the fact that, whereas the rods are endowed with great mobility and appear to act independently, as if each had a consciousness of its own, the latter are held together in masses by transparent interstitial substance (glœa), and usually form a scum or pellicle on the surface of the liquid.

The meaning of these facts seems to be this. It is obvious that, in every liquid in which successive generations of organisms grow in the way I have described, each generation must alter the composition of the liquid; and that this change may consist, not merely in the discharge into the liquid from the bodies of such organisms of the "waste products" of their vital processes, but also (in case any of the earlier generations, instead of continuing to live, are disintegrated) of the products of such disintegration; so that, in the latter case, it is quite possible that a liquid which was at first non-albuminous may, as the process goes on, contain an appreciable quantity of proteid matter. That any such formation of plasma actually takes place, cannot be asserted. All that we know on observation is, that the later generations differ, as regards their morphological characteristics, from the earlier, and that they alone possess toxic properties; so that two processes must go on side by side: a change in the composition of the liquid, and a corresponding change of the organisms which grow in it.

The question whether the chemical changes of the soil determine the morphological characters of the vegetation, or are determined by them, must remain open; for the scanty facts which we have before us admit of being explained either way consistently with what is known as to the origin of organisms. Thus it may be supposed either that there exist originally in the liquid a variety of latent germs which, as the soil gradually changes its characters, emerge in succession into activity, the moment of germination of each being determined by the adaptedness of the soil for its development; or that the successive generations of organisms are organically continuous with each other, the forms first produced being gradually modified under the influence of the gradual change of environment. Both of these theories are open to objection. Against the first it might be advanced that we have as yet no sufficient evidence of the plurality of germs;† against the second that so rapid a process of evolution is scarcely consistent with our experience of the process by which other organised forms are evolved. In relation to our present inquiry, it is of comparatively little moment which of the two views is accepted, so long as it is clearly understood that the relation between the evolution of *organised form* and the concomitant changes of *environment* is of such a nature that, while neither can go on without the other, neither can be said to be the cause of the other.

I mentioned a while ago, that the fact of the gradual development

of toxic properties in liquids which contain no nitrogenous constituents excepting ammonium salts was first discovered by Bergmann. The same line of inquiry has been pursued further by several of his pupils; and I am now going to ask your attention to some recent researches undertaken by one of them, Dr. Anders,* for the purpose of determining how far it holds true as regards these originally non-albuminous liquids, that (as has been shown to be the case as regards putrid infusions) the poisonous action is exerted independently of the vital endowments of the organisms which produce it.

Of the various methods of experiment employed by Dr. Anders for this purpose, the one which yielded the most interesting results was the employment of antiseptics, using the term in its physiological sense as applicable to any body which destroys or annuls the physiological properties of septic organisms and of their germs. But before I proceed to discuss the application of this method to the question at issue, it will be necessary to say a word or two as to the relative values of the various bodies known as antiseptics in destroying the vitality or arresting the development of septic bacteria.

The best known antiseptics, and those of which we are most certain, are chlorine, potassic permanganate, carbolic acid, and salicylic acid, and lastly, the camphor-like products obtained by the distillation of the essential oils of thyme and of caraway—thymol and carvol. We know by experiment that these bodies differ very materially in antiseptic, or as it is sometimes called, germicidal power. My friend Dr. Buchanan Baxter found that in a cultivating solution, of which the composition agreed very closely with that on the table, chlorine produced sterilisation in the proportion of 1 in 100,000, potassic permanganate in the proportion of 1 in 10,000, and carbolic acid only when in the proportion of 1 per cent. About the same time that Dr. Baxter's researches were published, an entirely independent investigation of the same question was conducted by Dr. Bucholtz.† His researches extended over a larger number of disinfectants (although they did not include potassic permanganate), and had this additional advantage, that the value of each disinfectant was determined with reference to two properties, viz., first, that of destroying the germinative power of the liquid used, and secondly, that of preventing or checking the further growth of the bacteria already growing in it. The results are exhibited in the table. It is seen that, as regards the relative values of chlorine, sulphurous acid, and carbolic acid, they agree very closely.

At the time that Dr. Baxter made his experiments, salicylic acid had scarcely taken its place as an antiseptic. It appears, indeed, to have been first experimented on with a view to its germicide properties by Bucholtz, who was led to think that it would probably be an antiseptic by the consideration of its constitution and chemical relations. Bucholtz tells us that his experiments were already concluded, when he was anticipated by the publication of the well known paper of Kolbe, on Salicylic Acid, in *Erdmann's Journal* (vol. x, p. 89). Kolbe discovered that salicylic acid had a very remarkable power of preventing, even when added in a proportion which did not exceed 0.05 per cent., the fermentation of beer, and this led him to make a number of experiments as to its influence in arresting putrefaction, from which it appeared that meat, urine, milk, and other things could be kept exposed an indefinite time when small percentages of salicylic acid were added to them.

It was on the basis of these facts that Dr. Anders proceeded in his investigation of the toxic action of a liquid of the same kind as that which yielded the poisonous scum to which I before drew your attention. It was necessary to show by experiment, first, that the material to be used was toxically active; secondly, that the dose of salicylic acid to be added to it was without physiological action; thirdly, that the liquid in question was completely sterilised (*i.e.*, that a cultivating liquid, to which a few drops of it were added, remained transparent although placed in a warm chamber at the proper temperature); and lastly, that it was still active, producing death in a few hours with the usual symptoms, after the addition of the antiseptic.

I have only to add that similar experiments were made with chlorine, of which the results were equally unequivocal. Here, as in the case of salicylic acid, it was shown conclusively that a dose of chlorine which was more than sufficient to destroy, and actually did destroy, the vitality of the living organisms present, left the virulence of the liquid unimpaired.

* Anders, Giftige Wirkung von durch Bakterien betrübte Nahrflüssigkeit, *Deutsche Zeitschrift für Chirurgie*, vol. vii, p. 1.

* Hiller, Untersuchungen über die Bacterien in ihre Beziehung zum menschlichen Organismus, *Med. Centralzeitung*, 1874.

† This objection is deprived of whatever weight might otherwise attach to it by the beautiful experiments of Professor Lister, which appear to prove that even a single drop of water may contain a great variety of germinal particles.

† Bucholtz, Antiseptica und Bakterien, *Archiv für Experimentelle Pathologie*, vol. iv, p. 1. Bucholtz found that, while carbolic acid prevented the development of bacteria when added to his cultivation-liquid in the proportion of half per cent., the same result was produced with 0.15 per cent. of salicylic acid, with 0.1 per cent. of carvol, and 0.05 per cent. of thymol. The percentages of the same bodies required to sterilise a liquid already containing bacteria were, for carbolic acid, 4 per cent.; for salicylic acid, 0.3 per cent.; and for carvol and thymol, each 0.5 per cent. It was for this reason that salicylic acid was selected by Dr. Anders for his experiments.