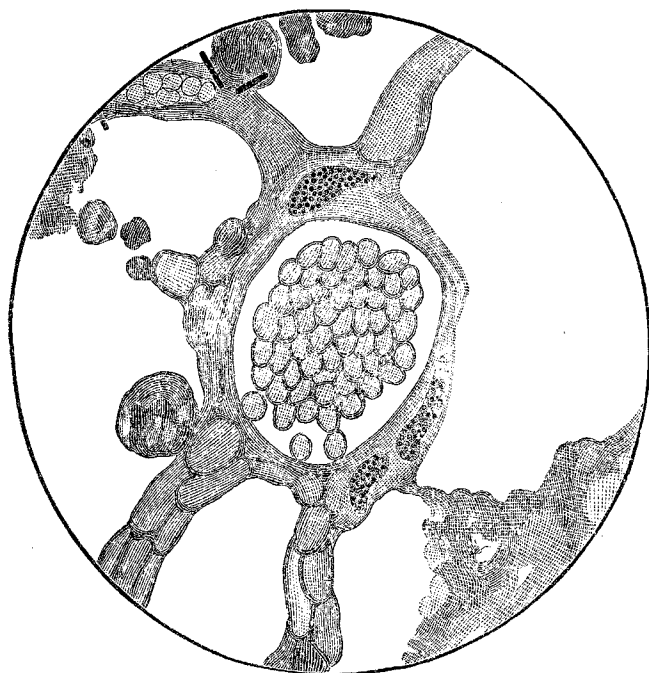


could not be seen with certainty. As the disease was of some days' standing this was not unexpected. The blood of the right auricle contained vast numbers of streptococci in short chains and entangled into masses. (Fig. 18.) Here and there the blood contained rather long, straight, or slightly curved bacilli, which were probably cadaveric. The lungs were enormously engorged with blood, and the air cells full of catarrhal exudation. Numbers of the smaller capillaries were plugged with micrococci. The emboli occurred in the capillaries of the walls of the air cells, and also in those in the walls of the pulmonary vessels and bronchi. (Fig. 19.) No chains could be discerned in these emboli, but none can be seen, as a rule, in similar emboli produced artificially by injecting streptococci into the circulation of rabbits. The

FIG. 19.



Streptococcus septicæmiæ. Micrococci in capillaries of the lungs. Two cadaveric bacilli are shown in the upper part of the figure. The blood contained others of the same kind.

kidneys were likewise engorged with blood, and the epithelium of their tubules was in an advanced state of cloudy swelling. Some of the smallest capillaries near the cortex and in the walls of the renal vessels were plugged with micrococci, as in the lungs; in the kidneys, however, the emboli were not so numerous. No bacteria were found in the liver, and the other organs were not examined. It is to be regretted that no examination was made of the heart. The clinical history seemed to show that that organ had not escaped the infection.

THE SO-CALLED ANTITOXIC TREATMENT OF INFECTIVE DISEASES, ILLUSTRATED BY DIPHTHERIA.¹

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DR. BERTRAM HUNT, after acknowledging his indebtedness to his friend Dr. Ruffer for having suggested to the Pathological Society that he should open the discussion, stated that he would deal with the subject in the following order: (1) a short glance at the history; (2) the bacteriology only so far as was necessary to a proper understanding of the production and nature of the toxin; (3) the result of introducing this toxin into animals with the production and nature of antitoxin; and (4) the pathology so far as it affects the prognosis of the treatment. The history divides itself into the prescientific and the scientific ages. The latter period may be said to have commenced with Pasteur, who discovered that protection could be conferred by artificial mitigation of

virus, the honour of which discovery is fully shared by Koch. In 1887 Salmon and Smith proved that not only mitigated bacteria but their products were able to confer protection, Sewall that immunity was possible to cobra poison, and Fodor that the blood was able to destroy bacilli. In 1891 Behring showed that if immunity to tetanus or diphtheria had been conferred upon animals their blood or serum was found not only able to protect other animals against either the bacteria or their soluble specific poisons, but even to cure them if injected subsequently to the virulent matter; and as a mixture of the serum with the toxin *in vitro* was found to be quite innocuous he called the serum "antitoxic," and the unknown substance in the same "antitoxin." In 1891 was published, too, what might be regarded as the first reading-book on this subject—namely, Ehrlich's work on the immunity conferred by feeding on animals against the vegetable poisons ricin and abrin. There are, therefore, two methods known of protecting against infective disease: (1) active immunity (more or less permanent) by the Pasteur method of introducing mitigated virus, with consequent slight illness, recovery, and protection against a virulent virus; (2) passive immunity (temporary only) by the Behring method of introducing mitigated bacteria or their products, with slight illness, recovery, and protection against a virulent culture or toxin, and the transference of this immunity to another animal by the injection of blood or serum taken from the first. In the first method the animal forms its own antitoxin; in the second it is previously formed in another animal and transferred as a therapeutic agent.

Production of the toxin.—Roux and Yersin noticed that a certain supply of oxygen to the bouillon culture increased the virulence of the toxin, which depended chiefly on the alkalinescence of the medium. It being troublesome to pass air through a culture, he (Dr. Hunt) had devised methods of obtaining bouillon surface growth whereby a virulent toxin is quickly attainable by floating powdered cork or little rafts made of cork wrapped round with wool and muslin, which serve as nutrient islands. The bacilli have an inveterate predilection to spread over a surface. The question of the action of oxygen on a pathogenic bacillus is extremely important and interesting. The virulent bacillus renders its culture media acid in twenty-four to forty-eight hours; the toxin is only found in an alkaline culture—and is, as he would suggest later, only soluble in an alkali. The action of the oxygen, in his opinion, was to prevent the acidity altogether, and although its free admission tends to encourage a merely saprophytic or non-pathogenic growth of bacilli, this disadvantage is more than counterbalanced by the maintenance of an alkaline reaction. Dr. Ruffer has found that cultures exposed freely to a supply of air do remain alkaline. Pasteur's classical experiments with yeast cells form an interesting comparison, for he found that surface cultures freely exposed to the air developed a vigorous yeast; yet there was little or no fermentative action, this only taking place when some of the aerobic cultures were afterwards cultivated anaerobically. There is no evidence that this exuberant aerated growth of bacilli has acquired any accession of virulence. In fact, as he (Dr. Hunt) had shown as regards methylene blue and the diphtheria bacillus a constant supply of oxygen, allowing of permanent reduction, is soon fatal to them. A free admittance of oxygen to the culture promotes, therefore, the growth of the bacilli, and leads to an early formation of the toxin, suggesting that the specific poison is some constituent of the bacterial protoplasm. Bacterial specific poisons were at first supposed to be ptomaines, and, although bacteria do many of them produce alkaloidal and other poisons, they are of no importance to the subject under consideration that evening, nor, indeed to any problem of immunity, in that they are not specific. Brieger and Fraenkel described a poisonous proteid which they called toxalbumen or proteid poison—an excellent name, as it implied a specific nature. In this country Hankin and Dr. Sidney Martin described the formation of albumose. The choice of the word albumose was unfortunate, for it was necessary to distinguish carefully between the vital chemical processes of the bacteria and of the action of these on their environment. Buchner had succeeded in growing tetanus bacilli in a solution of asparagine and in obtaining by precipitation a most virulent toxin. Experiments showed that toxin was elaborated not in the media but in the protoplasm of the bacteria—a proteid poison being formed in a solution containing no albumen, and that the production of bacterial poison was due to synthetic and not fermentative action. He would define, then, the diphtheria toxin as a specific proteid poison. But it must

¹ Abstract of a paper read before the Pathological Society on Tuesday, March 5th.

be clearly understood that it was not necessarily the proteid which was the poison, but what might perhaps be described as its disposition, its active and specific quality. Such active proteids had been called living proteids, and if this were adopted, then the toxic quality must be defined as the life in the proteid. The proteid having adherent to it this toxic quality is probably the myco-nucleo-albumen described by Gamaleia, a substance soluble only in alkaline media. This toxin, this vital chemical quality of bacterial protoplasm, was concerned in the metabolism of the bacteria, but it also constituted the offensive and defensive weapon of the microbe in its struggle for existence. He would say that in all living cells the protoplasm had this vital function. It was necessary, he thought, to regard the animal organism as a collection of pure cultures of cells of various types living together in harmony and in a state of complete chemical compatibility; as the forms of life fittest to survive in that particular environment the animal body; as resenting the intrusion of foreign substances, whether alive or dead, and with offensive and defensive weapons to maintain their existence, these weapons being chemical ones. In short, applying Darwinism to this question of immunity, we may consider the strife between the cells and the bacteria as a struggle for existence fought out between the synthetic vital processes arrayed on both sides. In animals which had a natural immunity to any infective disease it was obvious that the specific myco-proteid elaborated by the bacteria causing that disease must be either inoffensive or easily destroyed by the cells, and that it would occasion no struggle, no additional chemical activity in the animal cells—i.e., no constitutional or local disturbance. It ought not to be expected that such a body should be modified in any way, but merely excreted or quietly and quickly destroyed. In susceptible animals, on the other hand, there was a struggle, for a foreign proteid was introduced that was offensive and harmful to the animal organism, which organism, if it gained the upper hand, was able to yield us a substance of the highest therapeutic value.

Behring enunciated certain laws which must be obeyed in the process of immunisation. 1. It was absolutely necessary to wait until the animal had completely recovered before a fresh injection was given. 2. That the antitoxic value of the blood reached a maximum coincidently with this return to perfect health and then fell somewhat to a more or less constant level for a time. 3. That any fresh injection of toxin was best made when the antitoxin value was at its highest. 4. That the more susceptible the animal the greater the degree of immunity finally attainable and the more antitoxic the blood. 5. That the immunisation could be carried too far and a condition allied to natural immunity or a poison-proof state brought about. Behring chose the sheep, but their immunisation is a tedious process, and consequently Aronson and Roux chose the horse. Antitoxin was very different in its action to that of any modification of toxin *as yet known to us*. For it was therapeutic, whereas toxin mitigated by any of the ordinary methods if injected simultaneously with virulent toxin was found to accelerate the fatal termination. Antitoxin was, moreover, perfectly harmless, and the immunity which it conferred was immediate and temporary. Buchner had settled once for all time that direct antitoxic antidotal action of the antitoxin to the toxin neither took place *in vitro* nor in an animal organism, as had been maintained at first by Behring. The two substances—antitoxin and toxin—existed side by side, and no neutralisation occurred. Antitoxin, moreover, acted merely as a stimulus to the chemical processes of the cells, and if these cells be enfeebled in any way and their vitality lowered, the stimulus failed to rouse them and the antitoxin was of no avail. Just as in animals immune to diphtheria a curative substance was found in the blood, so presumably a similar curative substance must be obtainable in the case of all diseases caused by the invasion of the animal organism by any kind of cell foreign to it. A law, therefore, might be laid down that, whenever disease is set up by the invasion of any other form of life into the animal organism, immunity to such disease would confer curative properties on the blood of the immune animal. This curative quality of the serum in immunity to diseases had been designated as antitoxic only in tetanus and diphtheria, and not in the others, because the bacteria concerned in their production did not produce any definite specific poison for the serum to have been erroneously supposed to be able to neutralise. It had not been called

antibiotic because it was far easier to show that such serum possessed no antibiotic power than that so-called antitoxin had no antitoxic power. Hence, antibiotin has not been invented to describe such curative agents. It must not be supposed, however, that any possible increase of the natural germicidal power in the blood of the immune animal was denied, but it was only maintained that the substance here designated antibiotin had no antibiotic qualities in itself, and, as Buchner had pointed out, the serum of an animal might be deprived of its antibiotic or bactericidal quality by heat, and yet could retain its specific curative quality. In order to prove that antitoxic treatment was in reality a rapid process of immunisation it was only necessary to compare the action of these antibiotins with diphtheria antitoxin. (Reference was here made to Pfeiffer's experiments on the blood of animals immune from cholera.) The treatment of guinea-pigs with curative serum in experimental cholera injection might be defined as being merely a rapid immunisation method, so rapid as to be practically instantaneous, and there was no reason to doubt but that the action of antitoxin in diphtheria was precisely similar. The best way, therefore, to express the method and meaning of this process of protection was by calling these protective and curative qualities of the blood of immune animals specific immunising or curative agents.

Attention might now be drawn to the rapidity of the immunisation in diphtheria. In an ordinary poisoned wound of the finger the absorption of the poison could be traced along the lymphatic system. In simultaneous injection of diphtheria toxin and antitoxin the mixed solution must pass through the lymphatic glands, and in the presence of the antitoxin the cells were able to deprive the toxin of its injurious character, and, therefore, no illness resulted, and there might be no local reaction—in other words, a condition of immediate immunity would seem to be conferred on the tissues in which the injection was made. Buchner would seem at one time to have thought that antitoxin might be obtained directly from the bacterial protoplasm, but it must be considered, he (Dr Hunt) thought, to be either a direct or indirect product of the animal cells, either as a secretion or as an excretion. Buchner had given a valuable comparison between the bactericidal substance present in serum—namely, alexin, which was a direct product of the animal cells and the so-called antitoxin. Alexin was able to destroy bacilli, was very unstable, and varied with the species. Antitoxin, on the other hand, had no bactericidal action, could withstand a temperature of 70° to 80° C., was unaffected by sunlight or putrefaction, and never varied with the species of animal, but always with the species of bacteria through whose agency it was formed. Tetanus antitoxin cured tetanus, but not diphtheria, and *vice versa*, which was strong proof that these specific curative agents found in the blood of immune animals could not be direct products of the cells. Further experiments of Pfeiffer were adduced to show that the specific nature of the curative agents militated strongly against the assumption that antitoxin was a direct product of the cells. Moreover, natural immunity was not transferable, and it was impossible to bestow bactericidal power on the blood of one animal by the introduction of an efficacious alexin from that of another. A well-recognised direct secretion of cells was therefore not transferable. Antitoxic treatment of diphtheria was the successful transference of some curative agent and this distinction between alexin and antitoxin suggested that antitoxin was some foreign matter circulating in the blood of the immune animal. He defined antitoxin and the specific curative agents found in the blood of animals immune to infective diseases as being the specific proteids of the bacteria to which immunity had been attained, modified and digested by the cells, and that whatever their chemical nature was they must be considered as derivatives from such myco-proteids, still possessing some degree of their specific nature, but with a wholly beneficent character. To regard specific curative agents as being of this nature was to find an explanation of many otherwise most puzzling facts. If the conclusions arrived at were correct it should follow that if a series of animals was taken of all degrees of susceptibility, from one possessing a natural immunity up to an animal of the most extreme susceptibility, the further removed the animal was from the condition of natural immunity the more antitoxic the serum should prove; for in the very susceptible animal no destruction but only the requisite beneficent mitigation of the poison would take place. This was one of Behring's laws. One observation that militates against this conception of

antitoxin had been reserved because the answer to it afforded a clue to the way in which it was formed. Roux discovered that if a highly immunised horse was bled, and then subsequently bled without any intermediate injection of toxin, the second bleeding yielded serum with an antitoxic value equal to that yielded by the first bleeding. He (Dr. Hunt) thought the explanation of this was to be found in the phenomenon of cumulative poisoning (as for example strychnine), and cited a paper by Metchnikoff giving the results of experiments carried out at Dorpat in support of this. The cells of the horse become accustomed to the toxin, they begin to take it up and to slowly excrete it in the form at present known as antitoxin; but this process was a constant one, and much toxin was kept stored up in the cells, so that even if no fresh introduction of toxin was made the blood might yield antitoxin for a considerable time. Finally, antitoxin had certain physical similarities to the toxin which produced it, both being precipitated by entanglement, and both soluble only in an alkaline solution.

If antitoxin was merely toxin altered and excreted by the cells, how is its action as an excito-cellular stimulus to be explained? Buchner had shown that the injection of any proteid matter, foreign to an animal organism, increased the anti-biotic power of the blood, and Rumpf obtained distinct therapeutic results in typhoid fever by the injection of the dead bacilli of blue pus. Klein also found many dead bacteria protective against cholera. He suggested as an explanation that the specific myco-proteids had a quality or disposition hostile or injurious to animal cells. This quality might consist of some particular molecular arrangement or vibration. If the cells succeeded in conquering, in digesting, this proteid poison, they would effect this by causing an alteration of such molecular arrangement. This altered arrangement being the result of a cellular effort of a particular kind, and possibly bearing the mark of that effort stamped upon it, it might be conceived that whenever this altered substance was brought into contact with cells similar to those which had bestowed the fresh molecular arrangement upon it, a cellular effort identical with that originally excited would be instantly induced.

Dr. Hunt concluded by a reference to the pathology of diphtheria, and stated that the essential factor in prognosis is the amount of damage already done before treatment is commenced. He had found an extremely early fatty degeneration of muscle structure, and in particular of the muscles having most work to do (the heart and respiratory muscles), in guinea-pigs infected with diphtheria. The early appearance of this degeneration in experimental diphtheria was very important to the prognosis of antitoxin treatment, and explained how the best results were obtained by its early exhibition and how a larger dose may be necessary, if given later, to effect the necessary excito-cellular stimulus.

CASES ILLUSTRATING THE SURGERY OF THE KIDNEY.

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(Continued from p. 338.)

CASE 33.—A woman aged thirty years, single, was placed under my care by Mr. Malcolm Morris. The family history was a bad one; her father died from phthisis; her mother was alive, but sickly; two sisters were living, one sickly; all the other children, six in number, died young. The patient had been strong and healthy. Five years ago she began to suffer with pain over the left kidney, and had ever since had an attack about every six months, each successive attack being more severe than the former one. The last six months she had begun to lose health and feel unfit for her work. She never passed blood or matter in the urine. The urine examined on several occasions was normal, except that it contained a good many oxalates and a great deal of renal epithelium. There was on examination very marked tenderness over the left kidney, but I could not define the organ. The right kidney was large, smooth, and somewhat too mobile. Just

before I saw her she had begun to suffer with pain in the right side also, but it never began in the right side only when the pain in the left was severe. It was decided that I should explore the kidney, and I operated on Feb. 19th, 1890, and found a sacculated kidney, the cortex much thinned and pale, the pelvis and calyces much dilated, the ureter healthy, but so small as to be obviously inadequate. I removed the kidney, tying the vessels separately and ligaturing the ureter low down towards the bladder and dropping the stump in. The right kidney was large, smooth, and somewhat globular, but appeared to be quite healthy. The removed kidney weighed 2½ oz. This, again, appears to be a case of gradual destruction of the kidney from inadequate size of the ureter. The patient made an uninterrupted recovery, and I heard quite recently from Mr. Malcolm Morris that she remains in excellent health.

CASE 34.—A married woman aged forty-three years, the mother of thirteen children, the youngest sixteen months old, four of them dead, was placed under my care at the Samaritan Hospital by my friend and then colleague, Dr. Prickett. In the right side of her abdomen, in the situation of the right kidney, was an irregularly oval, smooth, and not very tender tumour about four inches long. She had never had any urinary trouble. The urine examined was of low specific gravity, but otherwise normal. Her father died from stone in the bladder; her mother was alive and healthy, aged seventy-four years; eight brothers and sisters were alive and well, some more had died from acute diseases. One aunt died from mammary cancer. Before the last confinement, twins, she was very large, and then first began to have pain in the right side, and when she got up noticed a lump there. I operated on May 28th, 1890, and found a sarcoma growing from the middle of the convex border of the kidney and not affecting the pelvis at all; it was apparently covered by the capsule of the kidney, and was separable from the kidney tissue, not infiltrating. Unfortunately, through press of work at the time I did not get it examined microscopically.¹ The patient was suffering before the operation from advanced phthisis, and this was, I think, rather accelerated by the operation, and she died at the end of July with a large cavity in the left lung and the right also beginning to break down.

CASE 35.—This patient was a woman aged forty-two years, but looking much older, single, and very delicate. She had never had any serious illness till April, 1889, when she had a severe attack of influenza, which laid her up for several weeks. The pain first appeared during this attack in the right side and hip, and then, while lying in bed, she noticed a considerable swelling in that side. When she got up she suffered much pain in the back on the right side, which was increased by walking. I found a large fluctuating tumour in the right renal region, which I believed to be a hydronephrosis, and advised its removal. The operation was performed on Dec. 1st, 1890, and I could find nothing to account for the hydronephrosis. The ureter appeared quite normal in size and arrangement. I tied the vessels separately and pinned the ureter out in the lower angle of the wound. She made an uninterrupted recovery, and remains well. In 1891 she wrote to me that she was feeling better than she had done for a long time. The pathology of a case of this kind is obscure. I think there must be some abnormality in the ureter which is not recognisable when the abdomen is opened—for example, undue length leading to kink in certain positions of the body. This would, of course, become accentuated when once the pelvis of the kidney began to distend, till at last it might be so bent upon itself that no urine escaped at all. Seeing, as I now do, a large number of renal cases in consultation, I am strongly impressed with the close association of the uterine displacements with renal troubles, and I hope before long to call the attention of the profession more decidedly to this subject. I have long been convinced that many healthy ovaries have been removed for pains which were really renal or ureteral; and I am sure there is another side to the picture, and that in a certain number of cases the whole attention is fixed on the kidney when the heavy displaced uterus is the primary ailment.

CASE 36.—A woman forty-nine years of age, a widow, was placed under my care by my old friend, Sir Joseph Lister. She had ceased to menstruate suddenly seven years earlier, and then began to have hæmaturia with pain in the right

¹ The specimen was sent quite fresh to the Royal College of Surgeons of England, but unfortunately does not appear to have been examined or kept.