Treatment of bacterial diseases / [Sheridan Delépine].

TREATMENT OF BACTERIAL DISEASES.

GENTLEMEN,—The intense excitement and the unbounded hopes created by the announcement that a cure for consumption has at last been found have led me to lecture to-day on a subject which I generally relegate to the end of my course of pathology. For, after discussing the various phenomena which are brought about by disease, and attempting to connect these phenomena with their cause, apparent or real, it is natural to try to explain why these causes do not always bring about the results which are observed only in a certain percentage of cases.

Effects of individuality, age, sex, family, race, species.—It is a matter of common experience that in times of epidemics persons equally exposed to infection are not all affected. The weak members of the community are generally more readily affected than the strong ones, the starved than the well fed, the intemperate than the temperate, the fearful than the fearless; but, apart from these often doubtful distinctions, some other influences must be at work in helping some to resist, for many a man or woman of weak constitution has been able to pass through plagues that had

carried away more than one of powerful frame. This resistance of some individuals to disease has probably at all times attracted the attention of men, and very early in the history of civilisation observations have been made which by gradual extension have led to some of the most striking triumphs of medicine. It will be my object in this lecture to show you how immunity to disease, at first supposed to be due to individual peculiarities or supernatural influences, has gradually become connected with certain external circumstances acting directly or indirectly. Among the factors which are generally discussed in medical books as influencing the liability or immunity of certain individuals to disease I may mention age, sex, family, and race. These, as far as we can see at the present time, havean influence on the occurrences of disease which is in many instances difficult to explain. Some facts, however, tend now and again to lighten our ignorance, and to show that even these apparently inherent qualities are perhaps the result of the transmission of acquired properties through generations of cells or of individuals. This will be more evident perhaps if, by extending our field of observation from one to several kinds, we consider how the immunity of certain species, orders, or even classes of animals is brought about. Take, for instance, the remarkable immunity of the fowl and of the frog to anthrax. At first sight it seems impossible to understand why a small animal like a frog or a fowl should be able to resist a disease that is so rapidly fatal to such large animals as the sheep, man, or even the ox. Pasteur, however, more than twelve years ago recognised that the difference of the body temperature of the various animals was enough to affect the development of the parasite. He immersed a fowl for two days in water, bringing the temperature down to 28° C., and showed that the fowl was as liable to anthrax as any

other animal. A similar observation was made later on by another observer, who by raising the temperature of a frog rendered it also liable to the disease. Thus it was demonstrated that certain conditions of temperature were necessary for the anthrax bacillus to attain its full virulence. What temperature does in these cases chemical products, special to certain animals, can also bring about in others. This is well proved by the influence of various culture media on the growth of micro-organisms. The presence of chemical compounds of well-known nature, even in very small quantities, has been shown by a great many observers to influence much the mode of growth of bacteria. It has even been proved that bouillon obtained from the muscular tissue of various animals, notwithstanding the absence of any very definite active chemical compound causing marked difference, gave cultivation media more or less suitable for the growth of certain organisms. I will only mention out of a large number of other observations the very recent experiments of Hippolyte Martin on the bacillus tuberculosis. This observer found that animals can be classified roughly in the following way, according to the ease with which the bacillus grows in bouillon made with their tissues: herring, oyster, mussel, monkey, horse, calf, rabbit, birds, dog, cat, rat. It would be difficult in the present state of our knowledge to ascribe these differences to the presence of any definite compound, yet it cannot be doubted that they are due to certain physico-chemical properties. We have thus distinct evidence of marked differences between animals of different classes, orders, and species; and if we admit the truth of the doctrine of evolution, we must admit that such differences are in great part the result of the influence of external circumstances. We might infer from this that differences between animals of the same

species, but of different races, families, sex, or age, are likewise the result of similar influences; we have, however, better evidences than these in support of the view that either extreme liability or immunity to disease may be acquired. Indeed, I shall be able to show you that it is the gradual development of that knowledge which has prepared men for the reception of Pasteur's discoveries, and of their recent momentous extension by Koch.

1. *Refractory state resulting from a first attack of certain fevers.*—It was very early recognised that after a first attack of many infectious fevers, such as small-pox, measles, typhus fever, &c., a second attack seldom occurred. This fact seems to have been observed more specially in connexion with small-pox, or at any rate to have led to practical application first in connexion with that disease. We learn that the *inducement of a first attack of small-pox* was an antique practice in Africa, Persia, and China, and that the method of inoculation was brought from there to Constantinople in 1673, and from that town to England by Lady Mary Wortley Montagu. The idea was evidently to produce a mild attack of the disease in individuals placed under circumstances most favourable to recovery in order to induce immunity. The practice, although open to serious objections, must have had no little success, and was much resorted to in the middle of the last century. Another practice which is not so rare as one might be inclined to believe is the *inducement of measles.* Many people are under the impression that unless children have had all the ordinary exanthematous fevers it is almost desirable that an opportunity should occur for them to have mild attacks of these fevers, and I have known of instances in which, one out of several children being attacked with measles, no attempt has been made to isolate the sick child,

for, it was argued, it was as well for the other children to have the fever also and be done with it as soon as possible. Since this has been done under the influence of a popular belief, I think I am justified in suspecting that the practice of inducing measles for protective purposes is far from uncommon, although not generally carried out by professional men.[1] Boeck and Sperino introduced about 1854 the practice of *syphilisation*, and these authors recognise clearly that this method is not only a prophylactic, but also a truly therapeutical one. The inducement of a certain disease in order to prevent its recurrence, and even to modify the course of an attack, was therefore a method early recognised in this century both in connexion with small-pox and syphilis.[2]

2. *Refractory state produced by inoculation of an allied disease less fatal, or of the disease modified by passage through another animal.*—Certain country people had early suspected that a disease affecting cows was communicable to man, and that individuals thus affected were not so liable as other people to small-pox. History tells us that an English farmer and a German schoolmaster in the course of the last century, under the influence of that belief, had resorted to inoculation of that cow disease in preference to the inoculation of true variola. Jenner was the first medical man who discovered the immense importance of these traditional beliefs and practices, and after devoting all his energy to the study of the subject became so convinced of the value of the method of vaccination that after a long struggle he has succeeded in convincing others, and

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[1] Home, Speranza, and Katona have actually inoculated measles.

[2] The same principle has been applied in the *Typhus contagieur* of cattle by Salchow according to Billard (1820), and in contagious peripneumonia by Willems, a Belgian doctor.

has become thus one of the greatest benefactors of the human race. From 1798—when Jenner brought vaccination before the world—up to 1880 very little was done to extend the scope of the principle thus discovered. Then Pasteur arose, who, after studying for many years the nature of the virus causing several diseases, became gradually convinced that this virus may become intensified or attenuated at will, and in 1880 was able to state positively that the production of an attack of definite intensity of many infectious diseases was a thing not only possible, but also practicable and capable of application for the prevention of disease. In 1880, also, Burdon Sanderson suggested that the attenuation of the virus of anthrax for the purpose of vaccination might be obtained by using the guinea-pig as an intermediate host. Greenfield experimented also at the same time and in the same direction with very satisfactory results. In 1883, Pasteur and Thuillier made experiments in the *rouget des porcs*, showing clearly that by causing the virus to pass through a series of pigeons it became gradually more virulent for the pig; whilst the reverse was true when series of rabbits were used as intermediates, showing thus at the same time how disease may originate or be modified. The principle of vaccination as introduced by Jenner seemed therefore to have become a fact capable of general application by this time. All that seemed necessary was to find a suitable intermediate host for the parasite. By growing the parasite in a series of such intermediate animals one was able to obtain a "vaccine" or "lymph," which, like that of vaccinia, was capable of inducing immunity, as well as an attack of the unmitigated disease would have, but without the same danger. Another fact of great importance has also been noticed by several observers—viz., that the occurrence of certain febrile affections may modify the course of

other febrile affections previously established. Daniellsen and Boeck were perhaps the first to notice this fact, and to record the beneficial influence which an attack of small-pox might have on the course of tubercular leprosy. I need not refer to the numerous attempts which have been made since in that line.

3. *Refractory state produced by inoculation of a virus modified by cultivation outside the body.*—Another discovery, more fertile in results, although similar in principle, was, however, made known by Pasteur in 1880. He showed that by cultivating the microbe causing chicken cholera at a temperature of 33°, with free access of oxygen, he could obtain in from two to eight months an attenuated virus, which would cause the disease in a form mild, but sufficient to produce immunity. Toussaint and Chauveau were experimenting at the same time on the anthrax bacillus. Toussaint made the important discovery that by heating cultivations of the bacillus anthracis rapidly to a comparatively high temperature its virulence was attenuated. In 1881 Pasteur produced attenuation of virulence of the bacillus anthracis by cultivation for nine days at a temperature of from 42° to 43° C., and produced immunity by vaccination with the modified virus. Koch, Gaffky, and Loeffler repeated Pasteur's experiment in 1884, confirmed his results, and extended them, differing from him only with regard to the influence which he attributed to oxygen. In 1882 Pasteur and Thuillier applied to the bacillus of "rouget" the same principle as that used in the case of the chicken cholera and splenic fever, and succeeded in attenuating that virus also. During the whole of this period Pasteur was occupied in trying to isolate the virus of rabies. Although he did not succeed in doing so, he discovered that the nervous tissues acquired in that disease virulent properties which indicated the presence

in them of some unknown virus. Not being able to obtain the virus itself, Pasteur used the nervous tissue as he would have a nutrient medium, and having discovered the method of obtaining spinal cords having a constant virulence (fixed virus), he dealt with these cords in the same way as he would have with ordinary cultivations, and thus succeeded (1885) in attenuating the virus and being able to produce immunity by vaccination, as in the case of the other diseases. Many other methods have been proposed for attenuating the virulence of organisms than those introduced by Pasteur. We have already seen how Toussaint and Chauveau used rapid heating. Paul Bert showed that oxygen under high pressure (20 atmospheres) kills the bacillus anthracis. Toussaint, Chamberland, and Roux (1880–86) added dilute carbolic, chromic, and sulphuric acids to nutrient med a for the same purpose. Klein (1888) used also very small quantities of corrosive sublimate for the same purpose. Arloing (1886) showed that bright sunlight has also an attenuating effect on cultivations in fluid media. It is useless to go into the further developments of these methods, that of Pasteur being the only one which has had very extensive application as yet as far as man is concerned.

4. *Refractory state produced by the introduction into the system of definite chemical products resulting from the action of pathogenic organisms on cultivation media.*— Salmon and Smith (1886) seem to have been the first to put into practice the injection of the products of growth of organisms independently of the organisms themselves.[1] They showed that the injection of cultivations of the microbe causing hog cholera produces the effects of attenuated virus after being sterilised. (It was, however, accepted before that time that micro-organisms generate

[1] See Note on page 14.

products which are deadly to themselves and are capable of arresting their growth, a fact which has also long been known in connexion with fermentation organisms.) Pasteur (1880) very early showed also that filtered chicken cholera bouillon injected into a bird produced the symptoms of the disease, although no organism was present in the fluid. He showed also that the same is true of the blood of animals affected with anthrax.

In attempting to explain the effects of inoculation with spinal cord for rabies, Pasteur also alluded in 1885 to the probable existence of some chemical compound in the cords which he used for protective inoculation, and suspected that this compound was instrumental in bringing about immunity. It was only about 1887 that these facts and views acquired fresh significance by the work of Toussaint, Chauveau, Wooldridge (1887), Chamberland, and Roux (1887–1888), on anthrax. Wooldridge, in a communication made to the Royal Society in 1887, reported that he had cultivated the anthrax bacillus in an alkaline solution of a peculiar proteid body obtained from the testis and thymus gland. The growth was not abundant, and after two days cultivation at 37° C. the bacteria were removed by filtration. *A small quantity of the fluid thus freed from bacilli, when injected into the circulation of a rabbit, allowed that animal to withstand the inoculation of extremely virulent anthrax blood.* All bacteriologists know the work of Charrin (1889) on the pyocyanic bacillus disease, of Chamberland and Roux (1887–1888) on acute septicæmia, &c., of Brieger, Chantemesse, and Vidal (1888) on typhoid fever, of Roux on symptomatic anthrax, and of Roux and Yersin (1888) on diphtheria. In most of these experiments the material used for inoculation was the cultivation medium modified by the growth of the organism, and sterilised either by heat, by filtration, or by

both methods. The work of Charrin (1889), Woodhead, Cartwright Wood (1890) has also shown that protection may sometimes be obtained not only by injection of the products of the growth of the pathogenic organism itself, but also of some quite different ones (bacillus anthracis and bacillus of blue pus).

The products used were therefore of a very complex nature, and it was not known to what kind of compound they owed their property of conferring immunity. Roux and Yersin had in 1888 tried to prove that their chemical virus of diphtheria owed its properties to an albuminoid body allied to unorganised ferment, but this last supposition is not generally accepted, although not disproved. (In order to understand the origin of the following improvements it is important to remember that the work of Panum (1856), Gautier, and Selmi (1873) had revealed the production of very poisonous alkaloidal substances during putrefaction. The more accurate researches of Nencki, and still more of Brieger, demonstrated clearly the existence of an important class of poisonous alkaloids produced by the micro-organisms of putrefaction. Gautier (1881), on the other hand, was trying to prove that animal tissues are also capable of producing by their metabolism poisonous substances of allied nature. The experiments of Lauder Brunton and Sir Joseph Fayrer on cobra poison (1873) should be kept in mind in relation with this subject. It was soon found that, besides these poisonous alkaloids, other more or less poisonous products might be manufactured either by animal or vegetable cells; these products were found to belong to the ill-defined class of albumoses. I need only refer to the work of Weir Mitchell (1860) and Reichert on the albumoses[1] of snake poison; of Sydney Martin on

[1] The term albumose was not used by these authors, but they described bodies having the reactions of albumoses and recognised their true affinities.

phytalbumoses—i.e., albumoses produced by vegetable cells, whether bacterial or others—an important work, which led him to infer later on that albumoses were products intermediate between the non-poisonous albuminous substances of the culture media and the most poisonous alkaloids. Büchner, Wooldridge, Hankin, and others were also discovering toxic albuminous substances in various fluids or tissues of the body, some of which were deadly to bacteria.) Returning now to preventive inoculation, we find that in 1889 Sydney Martin in London, and Hankin of Cambridge working in Koch's and Brieger's laboratories, had isolated from cultivations of the bacillus anthracis albumoses which were found by Hankin to produce immunity from the disease when injected into the body. Possibly under the influence of Hankin, *certainly later in the year*, the important researches of Fraenkel and Brieger on the toxalbumins of diphtheria, typhoid fever, cholera, tetanus, &c., were published. Thus, just as in the case of many remedies used for centuries in the shape of powders, extracts, decoctions, infusions, tinctures, &c., active principles have ultimately been discovered by chemists, *it was now found that out of the material used for the last ten years by Pasteur and his school, it was possible to isolate some active products of definite composition*, to which the lymphs or "vaccins" owe their prophylactic and curative properties. Such was the state of science when, in the course of last year, it was announced that Koch had found the means of curing phthisis by inoculation. All minds were to a certain extent prepared for such an announcement; yet the fact that one of the greatest scourges affecting human kind had at last come within the pale of treatment has created immense sensation. The little that is known of the treatment and of its effects seems to point clearly to the fact that Koch is using some of the chemical

products which have just been discussed, and therefore there is good reason to expect that *a certain amount of success* will attend the method. The results of previous experimenters show, however, that it would be wrong to hope too much from a system which has always been attended with *a certain proportion of failures.*

I have carefully avoided in this *exposé* to enter into many details, some of which are of great importance, in order that you should be able to follow the main line of observations and thoughts which have led to the recent discovery. I will therefore not attempt to discuss on what basis vaccination, essentially prophylactic in principle, may become a curative method when the modified virus answers certain requirements. There is a very distinct connexion between these two methods of treatment.[1] It may, however, be interesting to consider for a moment the methods which the knowledge of pathogenic organisms has introduced in medicine.

These methods can be subdivided into three classes: (1) The preventive, (2) the protective, (3) the curative. They have all something in common, and yet they all differ, as will be seen in the following brief enumeration :—

1. The *preventive method* consists in *destroying or attenuating the cause*, or avoiding it in some way or other so that the body may remain unaffected. (*a*) The *antiseptic method* introduced by Lister is a good instance of the methods which aim at *destroying the cause* before it has acted. (*b*) *Residence* in high localities, *drainage*, &c., are instances of the methods by which the causes of disease may be so

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[1] For explanation as to the mode of action of the products used in vaccination see Lauder Brunton's lectures on Chemical Structure and Physiological Action, especially Lecture II. (Brit. Med. Jour., vol. i. 1889, p. 1389).

attenuated or diluted as to become harmless. (*c*) *Absolute cleanliness. Aseptic* methods are based on the possibility of avoiding certain causes entirely without destroying them.

2. *Protection* consists in so *modifying the possible host* as to render it able to resist virulent parasites. This can be done either by (*a*) increasing its *strength* and activity, as by diet, warmth, functional activity, and other hygienic conditions (Wargunin); (*b*) rendering its tissues and fluids *unsuitable media* for the *growth* or *full development* of the parasite. *Inoculation* and *Jenner's vaccination* are good instances of that method, which has been further extended by Pasteur and others; (*c*) by establishing *tolerance* (Sewall, 1887).

3. The *curative methods* consist in *attenuating* or entirely destroying the virus causing the disease *after it has penetrated into the body.* (*a*) The *actual destruction of the parasite within its host* is apparently still a desideratum. (*b*) *Attenuation of the virulence* can be obtained by introducing into the blood and tissues some product either interfering with the full development of the parasite or modifying the tissues and fluids of the body so as to increase their resistance to the extension of the parasite or to its products. This seems to be the chief principle at the root of Pasteur's *vaccination* for hydrophobia, &c. (*c*) *Neutralising the physiological action of the virus by using its physiological antagonist.* Muscarin, for instance, may be antagonised by atropin. Lauder Brunton (1873) directed attention to the possibility of applying this principle to the treatment of cholera. (The same idea has been applied to the treatment of poisoning by snake venom. Wynter Blyth, 1877; Lacerda, 1881). (*d*) *Destroying and removing the substratum* or ground which has become contaminated by

the parasite. This is *apparently the view which Koch has taken of the action of his lymph.* The action of the product on the tissues is, however, of the *same kind as that of the substances used in some of the methods already mentioned,* but more intense, and Koch's views will probably have to be modified.

In this attempt to analyse the methods which have been proposed I have separated processes many of which may act concurrently. This is, however, of little consequence, for my object was less to give an account of any single method than to trace the development of the ideas which are at the basis of the treatment of bacterial diseases. In this way I hope I may have been able to show you how *science* prepares the way for the highest branches of the *art*—viz., *preventive, protective, and curative medicine.*

Note.—Both Toussaint and Chauveau had already affirmed the possibility of chemical vaccination. Toussaint in 1880 produced immunity to anthrax by what he believed to be a cultivation of the bacillus sterilised by heat. In the original lecture which had been prepared in a few hours after the reading of Koch's November communication, the date of Salmon and Smith's communication was given as 1883 instead of 1886. Salmon's paper in 1883 does not, however, refer to chemical vaccination. The paper which I had in my mind was the one to be found in the Proc. Biol. Soc. Washington, vol. iii., Feb. 22, 1886.