[FROM THE *PROCEEDINGS* OF THE PHILOSOPHICAL SOCIETY OF GLASGOW.]

# *Immunity to Infective Diseases: A Pathological Study in view of Recent Researches.*

By JOSEPH COATS, M.D., Professor of Pathology in the University of Glasgow.

[Read before the Society, 20th November, 1895.]

I DO not know that any explanation or apology is needed for addressing this Society on a pathological subject. It is unusual, but I may presume that, as a society, we claim to include all kinds of wisdom, and that there is nothing which has truth and fact in it that lies outside our scope. I thought also that it might not be unwelcome to some to get a glimpse into a field with which they are perhaps unfamiliar.

The subject which I have chosen—that of Immunity—has its important practical aspects, which have already been ably dealt with in this hall. I may at once warn you that the pathologist's point of view is that of observation and scientific inference, and not directly the practical one, although our subject itself is an illustration of how the practical often closely follows the scientific. To my own mind the subject is one of extreme interest as a mere matter of pathological study, and it is purely from this point of view that I have chosen it for to-night's discourse, in the hope that I may be able to impart to my audience some of the interest which I myself feel.

Immunity and susceptibility to disease may be regarded as the converse of each other. Immunity is non-susceptibility, and susceptibility is non-immunity. When we speak of any specific disease in relation to mankind, we imply a certain susceptibility on the part of human beings to that disease; but when we come to regard individual men, we discover an extraordinary difference in the degrees of susceptibility, and, conversely, in the degrees of immunity. These variations are most readily demonstrable and most easily studied in diseases whose causes are somewhat fully known, and such are some of these that belong to the group of Infective Diseases.

Infective diseases may be defined as those which, demonstrably or by reasonable inference, are due to the invasion of the body by parasitic organisms, mostly of microscopic size. The body is infected by these organisms; but, as the infection may come from the outer world and not from our fellow-men, there are many of these diseases which are not infectious, in the sense of being communicable from one person to another. I may at once make this matter clear by adducing an example of an infective disease which is not an infectious one, and for this purpose I shall choose tetanus, or lockjaw. There is frequently present in the earth of gardens, streets, and elsewhere, a microbe which, presumably, plays some part in the economy of nature in these positions. This particular microbe, when carried deeply into the tissues of a living animal, as it may be by a penetrating instrument or article polluted with dirt from one of the sources mentioned, will sometimes live on in the tissues and multiply there. As a product of its vegetative growth, it produces a poison, or, as it is now the custom to call such products, a *toxine*, of intense virulence. It is a poison which affects specially the central nervous system, producing symptoms often of a very violent character. The microbe remains local, and produces little or no disturbance, but it sends off its deadly products, which produce the symptoms of the disease. This microbe, like many others, has been cultivated in glass vessels, or, as it is briefly expressed, *in vitro*, outside the body; and when so grown, it produces the same poison as it does in the body. The poison can be separated from the "culture," and, when introduced into the body, it produces symptoms similar to those produced by the microbe when it grows inside the body. The microbes, whether of this kind or of any other, when they multiply in the bodily tissues and so produce diseases, are only following the natural course of their propagation, and the living body is merely a medium for their culture, just like any other material suited to the purpose.

But the body of a living animal is something very different from dead animal matter; and if the microbes are, as it were, indifferently carrying out the phases of their life-history, the living tissues are by no means the indifferent victims of their energies. The animal body is not a mere mass of flesh and bone, but is to be regarded as an aggregate of an incalculable number of living units, which we are accustomed to call *cells* or *corpuscles*. These, though much larger individually than microbes, are still of microscopic size. Each possesses its own separate vitality, and all the actions of the body, of whatever sort, are ultimately resolvable into cellular actions. We are therefore to regard the body as in itself a state, or union of states, in which there are myriads of separate individuals, bound together in one confederacy, but bearing various relations to the whole. It is into this great commonwealth of living units that the microbes intrude themselves, and we may well suppose that the cells are not indifferent to the invasion.

In the further study of this matter, it is necessary to separate carefully in our minds these two—the microbes on the one hand, and the toxines, which are their products, on the other.

Taking first the poisonous products of the microbes, it may be said that the symptoms of the various diseases concerned are the results of the action of the toxines on the living cells of the tissues. They may be produced artificially by the toxine without the microbes being present in the body at all, or they may be produced by the toxine acting on one part of the body, while the microbes are situated at a different and perhaps a distant part, as in the case of tetanus, already mentioned.

On the other hand, in regard to the microbes, it is to be said that those concerned in the production of disease are only a small contingent of the great class to which they belong. In regard to all microbes, there is an opposition on the part of the living tissues to their intrusion, and it is only those which successfully overcome this resistance that become the causes of infective diseases. The great bulk of the microbes prey on dead matter alone, and are entirely barred from any invasion of the bodies of living animals. Those which are capable of obtaining a footing may owe this power to different circumstances. In some instances it seems as if they owed their ability in this direction to their own inherent vitality, whereby they are able to resist the control of the living tissues. In the majority of cases, however, it seems more probable that it is due to the influence of their poisonous products that they obtain a footing in the body; that is to say, when a few microbes are introduced, as must usually be the case in the beginning of most cases, they, by means of their toxines, paralyse the opposition of the cells, and so secure their position for further growth. This is well illustrated in the case of the tetanus microbe. If the spores of the microbe, carefully freed (by washing or otherwise) from the toxine, be introduced into the tissues in quantities which are not too great, then tetanus is not produced. In order to obtain a footing, they require to be accompanied either by their toxine or by some agent which will damage the tissues whilst they slowly multiply. It is found that various matters, including the products of other microbes and substances of various sorts, are able to give, as it were, the start to the tetanus microbe, and that even a direct injury to the tissue may do so. It is obvious that, in what may be called the natural mode of acquiring the disease, dirt containing microbes of various kinds is introduced, and the tissues are injured, so that the necessary conditions for the growth of the microbe are furnished.

Such being, in the briefest possible sketch, the general facts in regard to the parasitic organisms which produce infective diseases, and the bodies of living animals, which are the seat of their energies, let us now turn to the subject which is more specially before us. From what has been said as to the relation of the living microbes on the one hand, and the living cells on the other, it may readily be inferred that there are differences amongst animals in regard to the various reactions of cells and microbes. Although the living structures of animals are all ultimately composed of cells, yet these cells have, in different animals, and in different parts of the same animal, variations in structure and endowment, and we are not surprised that these differences manifest themselves in this matter of susceptibility. Let me in a few words mention, in regard to tetanus, some of the facts ascertained as to the susceptibility of different species of animals to this form of infection. The horse is known to be singularly susceptible; so also is the guinea-pig; and, to a somewhat less degree, the mouse. The rabbit is still less susceptible, and the rat less than the rabbit. The sheep, the dog, and the pigeon are very slightly susceptible, and the domestic fowl is insusceptible to ordinary inoculation with the microbe. Each species of animal, with its inherited and inherent constitution, has its own specific relations to the parasitic organisms, which are the agents of infective diseases. The same applies in a less degree to the races and varieties of the different species, and in a still less degree to the individuals of each race. A striking difference in susceptibility as affected by race is exemplified in man in the case of yellow fever. The negro race is almost immune to this disease, which is so virulent in persons of the white races. It is also known that in the case of diphtheria, scarlet fever, typhoid fever, &c., there are striking family and personal peculiarities in susceptibility, and, conversely, in degrees of immunity. It is in this sense that we speak of Natural Immunity, which is part of the constitutional endowment of the animal, and depends, like the other items of his constitution, on inheritance.

If we inquire as to the exact significance of Natural Immunity, we are on more difficult ground. When microbes find their way into the body of an animal which is naturally immune, what is the precise method by which they are disposed of, so that the disease does not develop? It may be stated, at the outset, that it is not because the toxines are not poisonous to the animal. An animal which is immune to the disease as introduced by the microbes is quite susceptible to the poison introduced, with or without the microbes, as when the toxines are used. There is, of course, no proper infection; the disease is not established. It is simply a case of intoxication or poisoning; the symptoms depend on the dose of the poison, and disappear when the poison is exhausted. Natural immunity is a matter of the microbes in relation to the living structures of the body. The fact may perhaps be stated with sufficient accuracy by saying that, in the case of an animal possessing natural immunity to a particular disease, the microbes concerned in that disease are simply relegated to the same category as the great majority of microbes, which, as we have seen, are barred in their attempts to obtain a footing in the body. The modes in which the former are disposed of are, presumably, not different from those applicable to the latter. The manner in which the entrance of microbes is barred, and in which they are dealt with if they obtain entrance, is not fully understood. Probably there are many ways in which these objects are effected, and here, as in all the vital actions of the body, we must look to the active units of the body, the cells, for the explanation.

Some of the possible modes may here be mentioned. For one thing, the various surfaces of the body are covered with a close phalanx of cells, generally in several layers, and these, whilst effectively preventing the entrance of ordinary microbes in all animals, may in the case of immune animals prevent the entrance or lodgment of infective microbes. They may do so by the power which a living body has of preventing the entrance into its substance of foreign bodies, unless it takes them into itself for the purposes of nutrition.

Again, if the microbes get beyond this external boundary, the living cells may deal with them by taking them into their substance, nullifying them, and ultimately digesting them. This mode of disposal has been worked out with great industry and ingenuity by M. Metchnikoff, who has devised the name "Phagocytosis" for the faculty which many cells have of taking up and digesting particles of matter capable of being assimilated. The observations of Metchnikoff show that in the case of some of the best-known infective microbes, such as those of anthrax and of tuberculosis, when these are introduced into immune or partially immune animals, the living cells of the tissues take them into their substance, and dispose of them. The microbes undergo certain alterations in form and reaction to staining agents, and finally become assimilated by the cells.

Besides these modes, it is not improbable that the living cells may, in the presence of microbes, emit some substance which is capable of paralysing the microbes, and that, when thus weakened or killed, they may be taken up by the cells and digested. This has been asserted more especially in regard to the free wandering cells, which form an important constituent of the blood.

Again, it is not unlikely that in some cases the blood of an animal may be uncongenial by reason of some peculiarity in its chemical constitution to particular microbes. It is an ascertained fact that the blood-serum of some animals is unsuitable for the cultivation of certain microbes, although generally blood is a suitable medium. But this is not to be regarded as at all a general explanation of immunity, as the blood-serum of immune animals has in certain cases been found quite adapted to the culture of the microbes to which the animal itself is immune.

Another possible view is that in certain animals the cells may be less sensitive to the toxine, and the microbes are thus deprived in some degree of their aid in overcoming the resistance of the tissues. I may here recall what was said in regard to tetanus, in which we saw that the toxine, or some agent which acts on the tissues, is necessary, as well as the microbes, in order that the latter may obtain a footing. It is consistent with this that in animals which present immunity only in minor degrees, a larger dose of the agent will sometimes suffice to produce infection.

We may now leave the subject of natural immunity, with the remark that in it we are concerned directly with resistance to the entrance and propagation of the microbes, which are the infective agents, and that in this contest the active cells are, in some form or other, by their inherited endowments, the opponents of the intruding agents.

It is in the domain of Acquired or Induced Immunity that we have had of late the principal advances in our knowledge. It must have been early a matter of observation that, in the case of such diseases as smallpox, measles, and scarlet fever, a single attack conferred a high degree of immunity against further attacks. There is thus an acquired immunity. It was the knowledge of these facts that begot the idea of producing immunity to smallpox by actual inoculation with the virus of the disease. This was the first attempt at procuring what we may call induced immunity, which is obviously of the same nature as acquired immunity. This method of preventive treatment against smallpox is stated to have been of considerable antiquity. The modern knowledge of it dates from about the year 1715, and, curiously enough, it comes from the Turks at Constantinople. In that year, Dr. Kennedy, a Scotsman, wrote about inoculation for smallpox as practised in Constantinople. Its introduction to this country was, however, essentially due to Lady Mary Wortley Montagu, whose husband was ambassador at the Ottoman Court. She not only wrote to a friend in England describing the method, but, in the year 1717, she had her son inoculated, being the first British subject on whom the operation was performed. The matter taken from a smallpox patient was inoculated in one arm by Dr. Maitland, surgeon to the embassy, and in the other by an old Greek woman, who had been many years in the habit of inoculating. The disease ensued in due course, and there were about 100 pustules. Here was the induction of an actual disease (which generally occurred in a mild form, but was not without its fatal cases), in order to bring about immunity to the more virulent or fatal forms of the disease.

The introduction of vaccination by Jenner, in the year 1798, is the first instance of the production of immunity by the induction of a condition different from the disease against which protection is sought.

I suppose it is scarcely yet decided whether cowpox is a separate disease, or merely a modification of the deadly smallpox; but, whatever be its exact nature, there is no doubt that it confers an immunity which is probably less complete and less enduring than that conferred by smallpox itself, whether spontaneous in its origin or induced by inoculation.

From the splendid results of vaccination, attention was readily directed to the production of other diseases in a modified form, with the intention of affording protection from the virulent forms of the diseases. The ingenious and far-reaching mind of Pasteur, whose name will long remain the greatest in this line of research, was the first to bring into actual use the principles suggested by vaccination. It was in the disease of fowls, usually called fowl-cholera, that Pasteur first succeeded in producing artificially a vaccine, or, as he called it, an "attenuated virus." This disease is due to a small rod-shaped microbe or bacillus. It is cultivated artificially in glass vessels in the usual way, and, when inoculated in fowls, it produces an acute febrile disease, invariably fatal in one or two days. The bacilli are found in enormous numbers in the blood. It was found that when cultures of this microbe were left growing in glass for a long time, their virulence diminished greatly, so that when inoculated into fowls, the result was only a local and temporary disease, which the animals readily got over. And now, when fowls so treated were inoculated from a culture of full strength, they were found to be immune. Here, then, was an attenuated virus which acted like vaccine, in respect that a trivial and local affection afforded protection from a virulent and general one. Since these fundamental observations, which were published in the year 1880, a considerable number of infective diseases have, by various methods, been made to afford vaccines or attenuated viruses. Amongst the principal of these are anthrax, tetanus, diphtheria, hydrophobia, and cholera. The attenuation of the virulence has been attained in a number of different ways, besides that which Pasteur used for fowl-cholera. Thus, the mere cultivation artificially *in vitro*, if carried through successive generations without passing the microbe through the body of a susceptible animal, causes, in some instances, a diminution in virulence. On the other hand, a modification is in some instances produced by inoculating the microbe into an animal which is not very susceptible to that form of disease. Thus, in a disease of swine, called swine-erysipelas, which is induced by a small bacillus, a modified form of the virus is obtained by inoculating rabbits and using the microbes obtained from the bodies of these animals. This may be used to produce immunity in swine to the virulent form of the disease. Other methods which have been successfully employed are (1) drying for a longer or shorter period, as in the case of hydrophobia; (2) cultivation at higher temperatures, as in the case of anthrax, or at lower temperatures; and (3) the application of various chemical agents to the cultures before inoculation. These various results, to which I can only make the barest reference, you will recognise as the products of much diligence and ingenuity during the last fifteen years.

Of late a most interesting advance in our knowledge of the subject has been made in the demonstration of the fact that in the induction of immunity by the methods referred to, the necessary element is not the microbes, but their toxines, and that the microbes are quite unnecessary if their toxines can be obtained separately. I confess that, for myself, I was unprepared for this result, which reduces the matter of acquired immunity to a question of the action of poisons. The toxines are separable from cultures of microbes by various methods. It may be done mechanically by filtering through unglazed porcelain, or the microbes may be killed by means of heat, or by an antiseptic, such as carbolic acid. If this be done in such a way as not to alter the chemical character of the toxines, then the symptoms of the disease may be induced by injecting the products into the bodies of animals. You do not in this way produce the disease proper, as its infective character is gone with the absence of the microbes. You reduce the matter to a mere question of administration of a poison whose dose can be regulated. Beginning with small doses of the toxines, and gradually increasing them, a state of immunity to the larger doses can be induced, just as, when the habit of morphia drinking has been established, almost incredible doses of that drug may be taken with impunity. Animals rendered immune to the toxines in this way are also immune to the disease; that is to say, they are no longer accessible to the infective agents, and the most virulent forms of the microbes may be inoculated without result.

It is interesting in connection with these results to point out that immunity to other poisons is producible by similar means. The poisons of the cobra and rattlesnake have some resemblance chemically to some of the toxines produced by microbes, and immunity to these snake poisons may be induced by progressive dosage with the poisons. The same applies to the vegetable poison ricin, obtained from the castor-oil bean, and abrin, from the jequirity berry.

A still further, and even more unexpected, advance has been made in the discovery of what are commonly called antitoxines. When an animal has been rendered immune, either by using the infective microbes or the toxines, then it has been found, in the case of certain forms of disease at least, that the blood of the animal contains something which can be imparted to other animals so as to render them similarly immune. It is not necessary to use the blood as a whole. After some blood has been taken, it is allowed to form a clot, which, by contracting, squeezes out a clear fluid, called the serum of the blood, and this fluid contains the antitoxine, so that when injected, in relatively small amounts, into the bodies of animals of whatever species, it renders them immune to the particular disease concerned. This has been fully established in the case of two deadly forms of disease—namely, tetanus and diphtheria, and the results have been applied to the treatment of these diseases. In the case of diphtheria the procedure may be briefly described as follows:—The horse or the goat is selected, by preference, in order to obtain a supply of the serum. By a series of inoculations, either of attenuated cultures of the microbe, or of the toxine, in progressive doses, extending over some months, the animal is rendered absolutely immune to the most virulent cultures of the microbe of diphtheria. The animal so treated is bled so as to obtain some of its blood; the blood is allowed to coagulate, and is then left till the serum separates from the clot, and the serum can now be used for injecting into other animals, so as to protect them from diphtheria.

There is, again, a further stage in the evolution of this subject which is of the highest interest. The antitoxine in the blood-serum not only protects the animal when injected into its body, but it produces its effects when applied to the cultures directly. Cultures treated with the antitoxic serum are rendered innocuous, so that the antitoxine exercises its effects whether it meets the toxine inside the body or outside.

Now, it is not my business here to discuss the utility of these important discoveries in the treatment of disease. There can be no doubt of the facts attested consistently by a large number of observers of different nationalities. If the antitoxic serum can be administered to an animal at the time, or soon after the application of the infective agent, then the animal will recover, although an otherwise fatal amount of the virulent microbe has been administered. In the human subject the antitoxine can never be given at the time of infection, and, indeed, can only be administered when the symptoms show that the disease is established. It must be matter of careful observation to what extent the serum can effect the purpose after the disease has begun, and to what period of the disease its influence may extend. The case of tetanus is a somewhat peculiar one. The tetanus microbe is, as we have seen, introduced into wounds along with dirt carried in by the article which inflicted the wound. The microbe grows locally, but produces little or no disturbance in its local seat. It evolves its toxine, which, entering the blood, is carried throughout the body, and so reaches the nervous system, where it acts with extraordinary potency. The first symptoms, being those of irritation of the nerve centres, already proclaim that the poison is in the blood, and has begun its work. It is scarcely to be expected that, in this case, the administration of the antitoxic serum will be generally efficient. At the same time, its prompt application is said to afford some hopes of recovery.

It is different with diphtheria. In this disease, also, the microbe has a local seat, usually the parts about the throat, and it produces its most serious results by means of its toxine, which is carried into the general circulation. But the toxine produces important local effects, in respect that it sets up an acute inflammation in the parts mentioned. From this fact it results that comparatively early warning of the occurrence of the infection is given. Indeed, the condition of the throat may attract attention before any of the symptoms of general poisoning have developed. In this disease we may therefore reasonably expect better results from the use of the serum containing the antitoxine than in tetanus. The results of treatment are not as yet fully determined, but certainly there is very good promise of usefulness in this very fatal disease. It will be clear that an early diagnosis and an early application of the serum-treatment are essential, if success is to be obtained. It will be understood also that the treatment is used with great efficiency as a preventive measure in the case of persons exposed to the infection, as of members of a family in which diphtheria has broken out.

If, now, we look closely at the facts relating to induced immunity, we shall see that we have to deal with something quite different from natural immunity. We saw reason to believe that in natural immunity we have the more or less direct opposition of the living cells to the invasion of the infective microbes. Whether by phagocytosis or by some other method, the cells nullify the microbes, and so hinder the establishment of the disease. In the case of induced immunity, on the other hand, it is essentially a case of the products of the microbes, the toxines; and the microbes come in in a kind of secondary way. This kind of immunity is, in the first place, an immunity to the poison—an acquired tolerance of it, as may be said. When we speak of a tolerance of a poison being established by repeated doses of it, we are in the habit of thinking of the living cells as becoming blunted in their sensitiveness to the poison; but that idea seems to be an incorrect one, and, so far as the toxines of infective diseases are concerned, it seems rather that, in their opposition to the poison, the living structures exercise a more active function. They produce agents which antagonise the toxines, and the whole process seems, in its foundation, an opposing action of the toxines and the antitoxines. In the prolonged process of immunising an animal, the cells of the animal seem to be stimulated to produce the antitoxines in increasing quantities, and these appear in the blood serum, by means of which they may be conveyed to other animals. It is true that the immunity, which is primarily an immunity to the action of the toxines, also extends to the infective microbes, so that, when these are introduced, they do not produce their usual effects. The explanation of this will be considered afterwards, but meanwhile we may safely infer that it is a consequence in some way of the immunity to the toxines which has been brought about.

It might appear from these facts that the whole matter is one of chemistry—the antagonism, in a chemical sense, of the toxines and antitoxines. It is a mistake, however, in considering the action of poisons, to regard the matter from the point of view merely of chemistry. It is, no doubt, in some aspects, a question of chemistry, but it is the complex chemistry of living structures. This subject can scarcely be understood without some reference to the nature and action of poisons in general.

The peculiarity of poisons is that, in minute doses, they produce profound effects on the living units of the body. The cells, which are these active units, are in themselves chemical laboratories, in which the processes are continually going on. The poison, sometimes in excessively small doses, enters into and deranges the intricate vital chemistry of the cell, and so interferes with its function. This is something very different from the mere reaction of dead chemical substances in a test tube. It is consistent with this that the poisons have what is called a *selective action*. Each poison has not only a particular class of cells which it mainly affects, but the kind of effect varies in the different kinds of poisons. Thus, morphia selects the central nervous system, where it exercises partly a dulling and partly a stimulating effect. Strychnine also selects the nervous system, but concentrates its action on particular parts of it, where it produces intense irritation of the nerve centres. In their chemical nature the poisons are of various orders. We have the simplest mineral substances, such as arsenic; we have complicated alkaloids, such as strychnine and atropine; and we have albuminoids, such as the venom of serpents. The toxines of infective diseases belong chiefly to the class of alkaloids or of albuminoids.

The toxines of the infective microbes exercise their influence on the vital chemistry of the active cells, just as other poisons do, and they exercise their influence in similarly small doses. Those of tetanus and of diphtheria are toxalbumins, and hence, in their chemical constitution, they are related to that of the living cells, which are chiefly composed of albuminous principles.

As to the antitoxines, there are two possible ways in which they may exercise their protective influence. In the first place, they may, in some way, enter into chemical union with the toxine, as an acid does with an alkali, so as to produce a neutral or innocuous substance; or they may, in the intricate chemistry of the cell, exercise a protective influence by antagonising, in a physiological sense, the effects of the toxine. At first sight the former of these methods may seem the more likely. It is in favour of it, that, for example, when the antitoxine is added to the toxine outside the body, and the mixture is injected, the toxic effects remain absent. But, when we look more closely, this explanation becomes less probable. For one thing, the amount of antitoxine required to protect an animal seems to be small in proportion to the amount of toxine; and, for another thing, the amount of antitoxine required varies in the case of different animals, so that the same mixture will be poisonous in one animal and not in another. This scarcely looks like a case of chemical union or neutralisation. Moreover, an interesting observation by M. Roux, although it applies to the toxine and antitoxine of the venom of serpents, has evidently a determining reference to the case in point. When the toxine and the antitoxine are mixed before use, the venom fails in its effect, but, when the mixture is heated to 70° Centigrade, the virulence returns. It is as if there were here two separate substances, one of which was altered or decomposed by a temperature of 70°, and one was not.

We may, I think, infer that the second of the foregoing explanations is the correct one, and that the influence of the antitoxine is on the vital chemistry of the cells, just as is that of the toxine, but in a contrary sense. This conclusion seems to me, also, the more probable in the nature of things. The antitoxine is a product of the active cells, and it seems more likely that it should be related to the chemistry of the living structures themselves than to that of a substance produced by absolutely foreign agents. This view is strikingly reinforced by the important observation that in some instances one form of antitoxine acts as a protective against a toxine to which, in its origin, it bears no relation. Thus, it has been pointed out by M. Roux that rabbits rendered immune to rabies are also immune to the venom of serpents. This can only occur, so far as I can see, by the antitoxine of rabies acting as a protective to the living cells, enabling them more efficiently to resist the toxine of the venom. It is no true objection to this view that the antitoxine exercises its influence when mixed with the toxine outside the body before inoculation, because, in that case, both agents are introduced, and the antitoxine protects the cells just as if it were introduced separately.

If, then, the processes concerned in acquired immunity are those of vital chemistry, how are we to bring these processes into relation with the microbes in the actual experience of disease? The animal which has been rendered immune is protected from the toxines, and we may justly inquire—what becomes of the microbes which are the natural agents of the disease, and which in the actual cases are introduced into the body of the animal? There is, I think, no reason to suppose that because the antitoxine affects the toxine, it therefore acts on the microbes. On the contrary, I shall mention a fact later on which seems to indicate that in some cases, at least, the presence of the antitoxine has little or no influence on the vitality of the microbes.

How, then, are we to suppose the microbes to conduct themselves when introduced into the body of an animal which has been artificially rendered immune by the antitoxine? Well, it is perfectly clear that the microbes are only of consequence to the body by means of their toxines, and if the action of the toxines is neutralised, then the microbes cease to be dangerous. It is possible, as already indicated, that the microbes may sometimes proceed to multiply in the body in the presence of the antitoxine, but certain considerations render this unlikely, at least in most cases. The microbes of infective diseases differ from the ordinary forms, chiefly in respect that they produce toxines; but if they are deprived of the benefit of their toxines, then, I think, they may be relegated to the position of ordinary microbes. The toxine, in its local action, seems, as it were, to cover the advance of the microbes, and to give an opening for their multiplication. The living body in dealing with ordinary microbes by the means at its disposal, prevents them entering the tissues, and keeps them at its surfaces, where, indeed, they may be present in vast numbers, as in the alimentary canal and air passages. We may well suppose that the infective microbes, deprived of the advantages of their toxines, are similarily destroyed, or relegated to the mucous surfaces.

In order more fully to enforce what has been said, let us endeavour to picture to ourselves what the actual occurrences are, say, in the case of diphtheria, first in the process of rendering an animal immune, and next in cases where the serum has been used to protect a person on whom the infective agent has made its attack.

In rendering an animal immune small doses of the toxine are first administered, and these evidently stimulate the living tissues—that is to say, the cells—to the production of the antitoxine. With progressive doses the production of the antitoxine is augmented. It has been supposed by some that the antitoxine is, equally with the toxine, a product of the bacteria, perhaps even the toxine modified by the action of the living cells. This does not seem a probable view. The amount of antitoxine produced seems out of proportion to the toxine introduced. It is stated, for example, by M. Roux that it is possible from a rabbit immunised to tetanus to withdraw, by successive bleedings within a limited time, a quantity of blood equal to the whole blood of the body, and yet the serum will still retain to the full its antitoxic quality. The process of immunisation evidently stimulates the cells to the production of the antitoxines in increasing quantity.

And now, when this serum has been used to produce immunity in a person exposed to the infection of diphtheria, or in one who has already begun to show symptoms of the disease, let us consider what is the probable course of events. The microbe concerned in this disease exerts, by means of its toxine, a local as well as a general effect. It mostly has its local seat in the fauces, where it sets up a violent inflammation, accompanied by a certain amount of death of the tissues, and an exudation from the blood. The microbe is found growing abundantly in these morbid products, and there seems little doubt that the result of the action of the toxine is to afford pabulum, and, by paralysing the tissues, to favour the growth of the microbe. But if the antitoxine has been introduced, then these local effects are warded off, and the microbe is relegated to the position of ordinary microbes, and may or may not remain on the surface of the mucous membrane of the part. There is no reason to doubt that the microbe may live on, without producing any symptoms, in the throat of a person who has survived an attack of diphtheria, or who has been rendered immune by the use of the antitoxine. This introduces a most important consideration in the preventive treatment of such diseases. I have been informed by an undoubted authority on the subject that, in the case of a boy at a public school who had passed through an attack of diphtheria and was perfectly well in health, he found in the secretions from the fauces abundant virulent diphtheria bacilli nine months after the attack. This is quite consistent with what I have been saying, and it is a fact of great practical importance which must be taken into account in all efforts to remove the infection of this disease.

In this connection, and as illustrating some other points in the relations of microbes to infective diseases, I may cite one or two facts in connection with acute pneumonia, or inflammation of the lungs. This disease is due to a microbe which has its local seat in the lungs, where it produces an acute inflammation, just as diphtheria does in the throat. Like diphtheria, its toxines, passing into the general circulation, produce those serious symptoms —fever, &c.—which form the most important features of the case. It is a curious fact that this microbe, which is capable of causing not only pneumonia, but likewise several other forms of acute inflammation, is frequently present in the sputum of healthy persons. This is proved by the fact that, when ordinary sputum is inoculated into rabbits, in a considerable proportion of cases it produces similar effects to those produced by the coccus of pneumonia, and this microbe is found in enormous numbers in the blood of the animal. This virulent microbe is present on the mucous surfaces of many, if not of most persons, but is kept, as it were, at bay. It seems as if, by circumstances affecting the condition of the body as a whole, or perhaps of the lungs specially, the ability of the tissues to deal with the microbe were diminished, and it effects a firmer footing, and multiplies with extraordinary rapidity. It is also worthy of remark that at the point of time when a person with pneumonia "gets the turn," as it is said, the microbes do not suddenly disappear from the lungs, but are there virtually in equal numbers for some time afterwards. They have, almost suddenly, become innocuous, and the person goes on to recovery in spite of their presence.

And now, having carried you so far in the endeavour to comprehend a large subject within comparatively small limits, I should like to refer to one or two matters connected with the subject, one of which naturally arises in connection with what has just been said in regard to pneumonia. The facts relating to the production of the antitoxine go far to explain what has hitherto entirely baffled our comprehension—namely, the periodicity of certain infective diseases. How is it that smallpox, measles, scarlet fever, typhus, typhoid fever, pneumonia, diphtheria, and other diseases have a more or less definite period of time, at the expiry of which the symptoms gradually or suddenly subside, and the process of recovery begins? How is it, for instance, that in a case of pneumonia, you will one day have the patient in a high fever, breathing rapidly, and with an expression of extreme anxiety on his face, and the next day the fever has departed, the breathing is quiet, and the patient, though weak, is remarkably comfortable? In the condition of the lungs, which are the seat of the inflammation and the seat of the microbes, there is virtually no change, and yet the whole general aspects of the condition have altered.

The explanation is now perfectly plain. In the course of the disease a process of immunisation is taking place. The toxine, as it is produced and passes into the circulation, is, as in the artificial production of immunity, stimulating the living cells to the production of antitoxine. If the patient lives long enough for the production of antitoxine in sufficient quantity, then the action of the toxine ceases and the patient recovers. In the case of the several diseases which show this peculiarity of periodicity, each seems to have a particular time in which, on the average, the process of immunisation takes place, and so there are different dates at which the crisis occurs. When it does occur, then the toxine is neutralised in its action, and, although all danger is not past, as the organs may be organically damaged by the attack, yet the danger of direct poisoning by the toxine is over.

The immunity so acquired in the course of the disease is that which we know to exist, and to last for some time, when a person has passed through an attack of one of the diseases referred to—the condition which at an early part of this discourse I distinguished as acquired immunity. It is consistent with these inferences that the diseases having a natural period for their activity are also those in which a single attack confers immunity, for a time at least, from further attacks. The two things legitimately hang together.

It is interesting also, in this connection, to consider the limits which we may expect in the application of the treatment by means of antitoxines. Wherever there is a disease which presents in the individual cases a definite periodicity, and in which a single attack protects from further attacks, then there is a likelihood that an antitoxine will be obtainable as soon as it is found possible to induce the disease in animals. We already hear of the treatment of pneumonia with antitoxic serum, and more recently typhoid fever has been brought under observation in this respect. Unfortunately, most of the periodic diseases still baffle observers in regard to the parasitic agents in their causation. As soon as the infective organisms are isolated, cultivated, and used successfully in animals, we may expect to obtain definite results by the use of antitoxines.

But there is a class of infective diseases in which, I think, we can scarcely look for any results in this direction. These are diseases in which the infection continues, and shows little or no tendency to a spontaneous cessation, and we may infer that in these there is no production of an antitoxine by the living structures of the animal. This applies to the group of suppurative diseases due to the ordinary septic microbes. A prolonged suppuration, in which the toxines are constantly absorbed and produce most serious general effects, can scarcely come under the control of antitoxines procured in the way in which those of diphtheria and tetanus are obtained. The same applies to the most frequent and most disastrous of all the diseases of mankind—namely, tuberculosis. This disease, in its various forms, goes on frequently for years, without any sign of the person acquiring immunity. The toxine of it is the well-known tuberculin, but there is no known antitoxine, and none is likely to be obtained on the lines referred to. It is not that tuberculosis is a hopeless disease, even with our present knowledge, but that the way of cure is not to be looked for in this direction. We may even venture to hope that —as it is now made clear that the toxines are the potent and direct agents in producing the symptoms, and that these are capable of being antagonised by other substances—there may yet be discovered some agents which will act as antitoxines to the diseases mentioned, although not procured in the manner which we have described.

In conclusion, I would merely allude to the intense scientific activity which the subjects we have been discussing have evoked during the few years easily comprehended within the life-time even of comparatively young men. Pasteur's original researches into the process of fermentation were begun about the year 1857, and were prosecuted during several subsequent years. Lister began his antiseptic treatment, which directly flowed from Pasteur's observations, in 1865. Koch's method of procuring pure "cultures" was announced in 1880, and created, in itself, an immense advance. Behring and Kitasato definitely made out the existence of antitoxines of tetanus in the year 1890, and it is since then that all the important researches bearing on this part of the subject have been made. You will admit that it has been a most interesting, and at times a most exciting, period for those interested in such subjects to have lived through.