THE ADVANCE OF BACTERIOLOGICAL SCIENCE IN THE DIAGNOSIS AND PREVENTION OF DISEASE.

BEING THE INAUGURAL LECTURE
ON THE FOUNDATION OF THE NEW CHAIR OF PATHOLOGY
AND BACTERIOLOGY, MASON UNIVERSITY COLLEGE,

DELIVERED OCTOBER 9, 1899.

BY

R. F. C. LEITH, M.B., M.A., B.Sc., F.R.C.P.E.,
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To Sir Wm Gairdner
with best regards
R.F.C.L.

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THE retrospect of the history of this College is interesting from many points of view, and from none more so than from the side of its striking progress and advancement. Its expansion has been worthy alike of this great city in which it found its birth and has received its nurture, and of the great empire of England among whose academic institutions it has already gained for itself no mean place. The foundation of this chair of Pathology and Bacteriology, which the Council of the College have done me the honour of electing me to fill, is one of the most recent signs of this progress of which I speak; but although the chair is practically new and marks a very decided and important step forward, yet it should be noted that the teaching of the subjects which it professes does not begin in this College to-day. Much good work in both of its branches has already been done by the able men who, as teachers of Pathology, have preceded me here, and by others connected with this medical school who have been called upon to work in and teach pathological science at some period of their professional career. Some of this work has already borne good fruit, which has proved of value in the elucidation and alleviation of human disease and suffering. It is a source of great satisfaction to me to think that I shall have in my work here the great advantages of the co-operation of some at least of those able men as colleagues in this young and vigorous, and soon to be, I hope, highly successful and flourishing university.

"You go to teach a go-a-head science in a go-a-head place," was the remark of a friend to me the other day. This is unconventional language, but it is terse and true. It hardly applies to Pathology in general with the same force which it does to its handmaiden Bacteriology. The former is old and has less room in which to make advances, the latter is young and possesses vast unexplored territories. Bacteriology and Birmingham, though now closely knit together in friendship, are not of equal age. At the beginning of this glorious era of our good and gracious Queen's reign, Birmingham was already a city of considerable size and influence, while Bacteriology was yet an unborn babe, not to see the light for fully thirty years thereafter. To-day, however, both are giants. Both have recently shown a rapidity of growth and vigour of development such as human experience has rarely known, and both hold out immense prospect and promise of future great achievements. Birmingham supplies the world with its best and most deadly of small arms, but they do not surpass those which Bacteriology supplies to disease either in precision or fatality. In this fortuitous emulation of these two conquerors, the city and the science, I will not run the risk of deciding who has so far won. If the phrase pathology and bacteriology as applied to the science of disease be accurate, you can draw your own conclusions, for we do not yet say England and Birmingham when we refer to this country. Everyone thinks that he knows something about Bacteriology, especially when the more homely name of germs is used, but few outside the pale of the medical profession claim to know anything about Pathology. Even the medical man himself harbours not a few fallacies about it. It is so much associated in his student-mind with *post-mortems* and dead tissues that he comes to look upon it as chiefly coming in when life has gone out. There could be no more grievous error. It has really nothing to do with death. It leaves that to its confrères Medicine and Surgery! It deals only with disease and disease is essentially a phenomenon of life. There can be no disease in a dead body. It is only its results that are there. Pathology is therefore concerned with morbid processes, which take their origin and run their course within the living body. Bacteriology is but its offspring and its various facts and phenomena, theories and speculations can be completely appreciated and properly appraised only by the trained pathologist. It is true that there are now many well equipped Bacteriologists, highly skilled in technique, experimentation, and other divisions of this many-sided science, who are not pathologists. They are simply limited specialists, who cannot so well as the Pathologist widely grasp, rightly weigh and balance, digest and estimate the truths and the teachings of the science as a whole.

It is some of the more recent and important of these that I wish you to consider with me to-day. The accurate recognition of the true nature of any disease is all important in relation to its treatment and prevention, and no science has won greater victories or secured more brilliant triumphs in any field of labour, than Bacteriology has gained in this. Great as its achievements have been in the past, there is every promise that they will be greater still in the future.

THE PRODUCTION OF DISEASE.

In order to properly understand the facts which I am now going to place before you, it will be necessary to refer shortly to the role played by bacteria in the production of disease. Disease is caused by the multiplication of the living organisms in the tissues and by the production therein of poisonous products, conveniently referred to as toxines. The latter are the chief if not the only efficient factors in the great majority of cases.

THE PRODUCTION OF TOXINES.

Few substances have received the attention that has been bestowed upon these products by scientists, and so complex have they proved to be, so subtle and intricate in their reactions, that we still remain much in the dark concerning them. We have not so far been let into the secret either of their production or of their exact composition. We know that they are produced by the bacteria, but we do not know how. It is obvious however, that their production may be accomplished in a variety of ways, and we are not without evidence apparently supporting them all. *Vide* Fig. 1. We have first the supposition that they are formed within the protoplasmic bodies of the bacteria themselves, *i.e.*, intracellular, and either capable of being excreted in a modified or unmodified form, or incapable of being so excreted, requiring to be retained within the bacteria during their life time, and only being set free at their corporal death and disintegration. In the course of any disease a considerable quantity of any such toxines would naturally be set free, as large numbers of the germs are always dying. We have next the supposition that the toxines are formed not within the protoplasmic bodies of the bacteria, but outside them, in the fluids and tissues in which they lie, as the result of the changes which occur therein through the germs living upon them, *i. e.*, that they are of extracellular formation. For instance, if a culture of a bacterium, say diphtheria, in bouillon be filtered through a porcelain filter, the germ free filtrate will, if certain precautions have been observed, be found to be highly toxic and able on injection into an animal to produce the symptoms characteristic of the disease. These toxic properties may have been acquired by the bouillon as the result of the bacteria living upon its constituents or as the result of direct excretion by the bacteria themselves; or further, the first substances produced may be of the nature of ferments, small in amount and powerless of themselves to do much harm, but capable of great after-effect in virtue of their digestive action, which when fully established comes to confer upon the fluid in which they are present toxic properties of great power. It is therefore apparent that we cannot draw any hard and fast line between intra- and extra-cellular toxines. In individual instances one or other method of formation may be predominant, but in many they may be combined. Further, more than one toxine may be formed by any one bacterium, or it may be that the particular toxine formed by any bacterium, is so complex and so unstable that it readily breaks up into bodies varying very much from one another, especially under different conditions of formation. We must, for instance, carefully refrain from the supposition that the toxines which a bacterium forms in artificial conditions of growth are necessarily identical with those which it produces in its natural habitat within the animal body.

SPECIFIC ACTION OF THE TOXINES UPON THE TISSUES.

While then we cannot be said to know much about their method of production, yet we do know that they exert a specific action upon the body and its tissues. They act not only locally upon the tissues, giving rise to characteristic lesions, but also generally upon the system, causing, through their absorption into the circulation, characteristic symptoms. When bacteria gain an entrance into the body they do not all cause these characteristic symptoms to appear at the same time; some appear sooner, some later. We say they have different lengths of incubation period and it is possible that the explanation of this is to be found in their different methods of toxine production; those, in which the toxines are directly and freely excreted as such, shewing a short incubation period, and those in which ferments are first formed, or which act chiefly through poisons of intracellular formation, having a longer one according to the time taken for the establishment of the various stages of the digestive action, or the liberation of the intracellular poisons in sufficient amount.

THE NATURE OF THE TOXINES.

We cannot be said to know much about the nature of the different toxines, although it is certainly a good deal more than about their method of formation. We do not yet know the exact composition of any single one of them, for not one has been isolated in a pure form. We know however that, though all differing from one another, they all belong to a well-defined group of poisonous substances possessing well-marked and similar properties. Other members of this group occur freely, both otherwise in the vegetable and in the animal kingdoms. We need only mention in illustration ricin and abrin, two vegetable poisons of great potency, and snake and scorpion poisons. It is not necessary to enter into any detail regarding the characters of this great group We know a good deal about the similarities and differences of its members, but we have yet to learn much about the individual toxines themselves. There is every probability that their composition and conditions of production are even more complicated than any result we have so far been able to obtain by practical experiments, or even aim at by reasonable theoretical suggestions. Marmorek recently informed me that he believed he had hit upon a reason why the streptococcus as ordinarily cultivated produces so little toxine. The amount of toxine produced by any given culture is usually so small in comparison with the number of germs present as to suggest the presence of some inhibitory substance of early appearance and extracellular position. *Vide* Fig. 2. He found that while the germ free filtrate of such a culture possesses very little toxine, it will yet prevent the growth of fresh streptococci, for if these be added to the filtrate they do not grow, whereas other organisms, *e.g.*, typhoid, plague, cholera, etc., flourish readily. This substance is produced by the streptococci and its presence stops their specific action, in other words, their toxine formation. They have not lost this power. It is only in abeyance, and the removal of the substance would quickly result in more toxine production; but it would appear to be of coincident or nearly coincident formation with the toxine itself since the production of the latter again soon comes to an end. By its successive removal it becomes possible to obtain the full amount of toxine production, and it is very considerable, from any given culture. He has not yet succeeded in isolating this substance, and he knows nothing as to its nature, beyond the fact that it is inimical to the growth and development, and hence to the disease producing power of its own organism. If further experience should show that not only the streptococci, but many other germs have this action, which we may term for the present a dual one, and always or sometimes produce extracellular substances inhibitory of their own powers of multiplication and toxine formation, it will open up new views on the subject, and still further complicate its problems.

THE DEFENSIVE POWERS OF THE BODY.

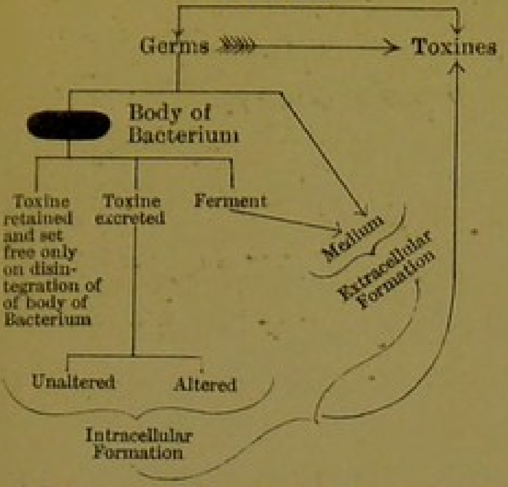
The toxines of bacteria, whatever their true nature, are certainly their offensive weapons, and they are arms of long distance range. By their means they wage war against the general bodily health. It is not, however, a one-sided fight, since the tissues possess considerable powers of defence, which are called into requisition whenever a bacterial invasion occurs. These defensive or actively resistant powers exist naturally within the body at the time of birth and are capable of and usually undergo great reinforcement as time goes on. They may come indeed to be so strengthened as to be able to successfully repel and resist certain bacterial invasions.

Pathologists are pretty generally adopting the belief that practically all disease is bacterial in origin. They are no longer satisfied that chills, fatigue, etc., can of themselves produce it. Such agents are no doubt powerful enough in deteriorating and so reducing the vitality of the tissues that disease may set in shortly after their incidence. They must be regarded, however, as able to act only as the predisposing and not as the exciting causes. They so weaken the natural resisting powers of the tissues that the latter, more or less easily, fall a prey to a bacterial invasion, which would otherwise prove harmless. An enquiry into the characters of these resisting powers is therefore of supreme importance to the life and health of the whole animal creation. A very large amount of most valuable work has already been done in this direction, but much remains to be done. So many are the able workers in this field, so earnest, vigorous and persevering are their efforts, that we may safely prophesy that the future, and we hope it is near, will disclose many secrets of the greatest value to mankind. It is too intricate a subject for us to attempt to enter into in any detail at the present time, but we may with advantage refer to its main facts and its more established doctrines. The chief, if not the only way, by which increased resisting power may be brought about, is one which does not at first sight appeal to us. It savours too much of locking the stable door after the steed has been stolen, but its aspect changes when we come to examine it more closely. The underlying principle is that one attack of a disease, from which an individual recovers, protects him from a second attack of the same disease. It is, unfortunately, not a general protection, but special only for each particular disease. Thus one attack of measles, scarlet or typhoid fever will generally be found to protect the individual from a second attack of the same disease, but not from the others. This applies, so far as our experience goes, to a very large number of diseases, and for this result to be obtained it is not necessary that they should be acquired by a natural process of infection. Artificial inoculation of any disease, either in its ordinary or modified form, is equally efficacious. This has long been empirically known and practised in the case of small pox. Immunity to this disease is given not only by a previous attack in its ordinary form, either naturally or artificially acquired, but also by Jennerian vaccination. The inoculation of the virus taken from a small pox pustule, especially from a mild case, was often practised before Jennerian vaccination was discovered, and it was generally successful in producing the disease in a mild form and in protecting the individual from a future attack. In Jennerian vaccination the lymph is taken from a case of cowpox, which is merely the same disease in a modified form. It has now been practised for about 100 years and at the present day is in extensive and general use all over the world. Its protective efficacy is undoubted, and it has completely gained the confidence and support of everyone, except a very small minority of very prejudiced individuals. The protection afforded by these three methods is the same, differing in degree only, being, as was to be expected, greatest in the natural disease, less great in the ordinary cases artifically inoculated, and least in the vaccinated ones.

The principle involved in Jennerian vaccination was followed out by Pasteur with brilliant results, and it has since formed the basis of an immense amount of work in a similar direction, which has already proved abundantly fruitful and productive. This

FIG. 1.

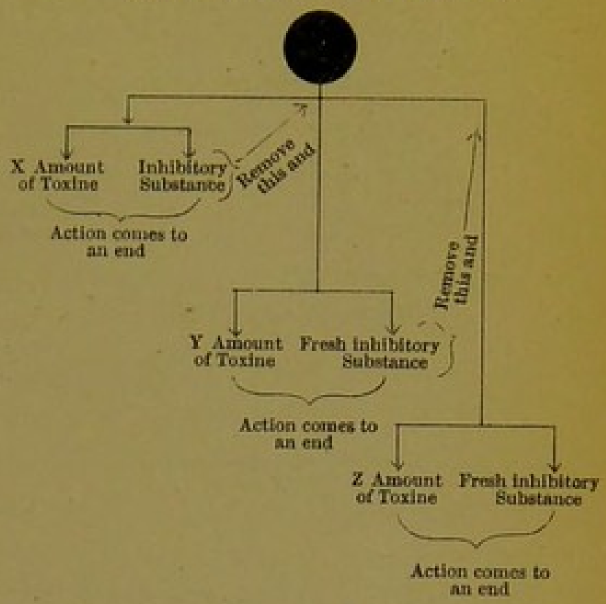
DISEASE.



Schematic view of the method of production of Toxines by Bacteria.

FIG. 2.

STREPTOCOCCUS CULTURE.



Schematic view of a probable action in regard to the amount of Toxine produced by any given culture of Streptococcus.

FIG. 3.

PROTECTIVE POWERS OF THE BODY.

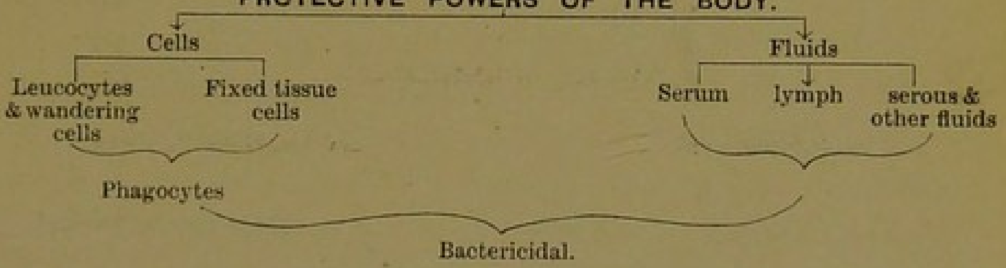


FIG. 4.

KINDS OF IMMUNITY.

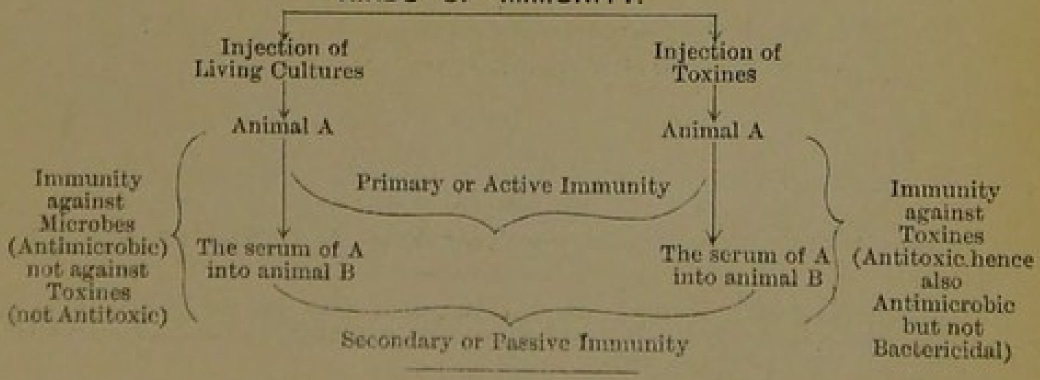
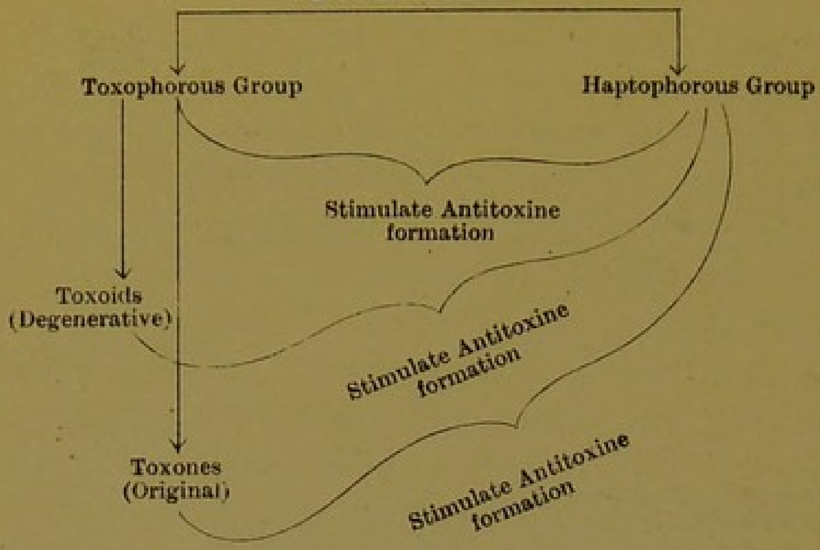


FIG. 5.

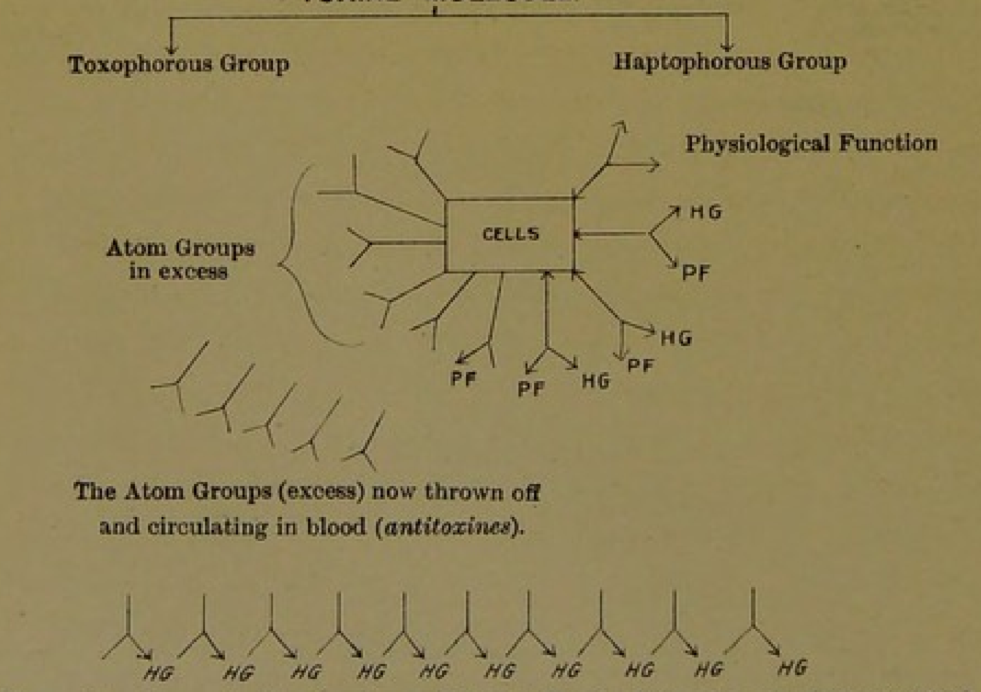
TOXINE MOLECULE.



Schematic view of action of the Toxine Molecule.

FIG. 6.

TOXINE MOLECULE.



These Atom Groups (antitoxines), now linked to Toxine Molecules, circulating in blood.

Schematic view of how the Toxine Molecule can act only when united to a cell by its Haptophorous group; how Antitoxines are formed, and how the Toxines are harmless when united to them.

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has suggested the possibility of the existence of the general law, that immunity to all diseases may be established for man by treating him with their specific viri, so modified as to be in themselves harmless. We have thus come to be provided with a number of prophylactic lymphs in relation to certain diseases which have already given much success and promise. Our knowledge of the causal relation which certain bacteria bear to certain diseases has enabled us to work in this field with far greater success than we could otherwise have won. We can produce many specific diseases at will, and in such a way that their severity, course and progress, remain entirely under our control. We aim at the production of a mild form of the particular disease, and this we can do with certainty in a variety of ways. 1. We may inject the living organisms in an attenuated condition of virulence. Such attenuated cultures are generally known as vaccines, as the principle is obviously the same as that of vaccination. It is capable of very wide application and has already given excellent results in a number of diseases.

2. We may inject the living virulent organism in non-lethal doses. The virulence of any organism is constantly undergoing change, generally towards attenuation, but we are able in various ways to restore it to its original virulence or even to greatly exalt that virulence. By preparing a series of cultures of the same organism of varying virulence, commencing with attenuation and ending with exaltation, we are able to graduate the dosage at will. These two methods may be combined with advantage. Experience has now shown it to be generally best to begin by injecting an attenuated culture and to employ doses of gradually increasing strength and virulence in subsequent injections, until at the end a high degree of virulence has been reached. In this way a high degree of protection may be arrived at. Cholera gives us a good example. In the human subject, two and sometimes three inoculations with the attenuated virus are made before the virus *exalté* is used. It is known as Haffkin's method and has been extensively used in India during the last five years with encouraging results. The

Pasteurian and likewise the Italian method of producing protection against hydrophobia is carried out in a similar manner, although as yet, it is empirically used since we know nothing of the *causa causans* of that disease.

3. We may inject the toxines from which the bacteria have been separated by filtration. These toxines can have their strength diluted or concentrated by various means. We generally begin by injecting small non-lethal doses of the strong toxine or larger doses of the attenuated toxine. Doses of increasing strength are then used. This method is also capable of very wide application, and immunity of a high degree can be obtained by it. Its greatest triumphs so far have been obtained in diphtheria and tetanus among the more commonly occurring diseases, and also in the case of snake poisons. It was thought for a time that equally good results might be procured through the administration of the toxins by the mouth instead of by injection; but notwithstanding Fraser's success with snake poison, and Ehrlich's with ricin and abrin, the two vegetable poisons already mentioned, where animals have been made immune to an injection of many times the lethal dose by previous feeding with these poisons, no practical use has yet been found for this modification of the method.

4. We may inject the toxines along with their microbes, having previously destroyed the vitality of the latter alone by some physical or chemical means. We here make use of the poisons residing within the bodies of the microbes in addition to their extracellular toxines. Haffkin's prophylactic against plague, which has given such successful results, is prepared in this way. He may be said to have diminished the mortality from plague by about 80 per cent.; an estimation based upon over 100,000 inoculations in the human subject, and thus to have saved thousands upon thousands of human lives. There are yet other methods, differing from one another, as these do, in important details, but, although so differing, they all agree in that they introduce into the body the specific morbific agent in such a modified form that while it is harmless for evil it is yet

productive for good. It is obvious that while the question of dosage is an all-important one in all the methods, extreme exactitude is of necessity of far greater moment when the living virulent bacilli are used than when the dead bacilli and their toxines are employed. The immediate effects which follow upon the entrance of any of these morbific agents into the body, depends not only upon the nature of the agent and the extent to which its powers have been modified, but it also further depends upon the particular animal employed. Animals may behave in a very different manner to the bacteria themselves and to their toxines, some showing little reaction to a large dose of the former and a great reaction to a small dose of the latter, and *vice versa;* others again reacting severely to both, or not reacting at all to either. The subsequent immunity thus produced varies also with all these factors, but more especially with the particular kind of animal employed, some showing a high and lasting degree, others less, others slight or none, and some even apparently a greater susceptibility than before. These facts, while they do not negative the universal application of a general law that the acquisition of an artificial immunity is always possible, yet make its acceptance, at the present time, impossible. It is more than probable, however, that these limitations have arisen through our present imperfect knowledge. We have not got the desired results because the paths by which we have sought to reach them have been faulty. The methods at present at our disposal have given us excellent results in some animals and in some diseases, but it may be that other methods of which we are yet ignorant are required for other animals and for other diseases. We may assume that a method which is good for any one disease in any animal will prove equally efficacious for the same disease in another animal, or for a different disease in the same animal; but if we find the assumption to be wrong, we are not entitled to say that the same results are not obtainable. We may yet come to obtain them by the use of other means.

The resisting and protective powers reside within the cells and general fluids of the body. *Vide* Fig. 3. It was for a time thought that the cells, the leucocytes and many of the connective tissue cells, possessed the whole of these powers, and the theory of Phagocytosis, one of the most brilliant and fascinating doctrines ever promulgated, was elaborated with masterly skill by Metchnikoff to explain how immunity was brought about. The cells were thought to be doughty warriors of great fighting power, and often extreme activity, ready at all times to wage implacable war against their bacterial enemies. It was thought that when hostile bacteria invaded the tissues, the leucocytes and wandering cells sallied forth from the blood-vessels, etc., in countless hordes, to give them battle, and that if the victory went to them the individual escaped; whereas if it rested with the bacteria, he became a prey to the specific disease they are capable of producing. There can be no doubt that the phagocytes, as these cells are called, play an important part in the establishment of protection. They have the power of ingesting germs and retaining them within their protoplasm, and that not only after the latter are dead, but while they are still alive and capable of producing their specific effects. They cannot, however, any longer be regarded as the sole protecting agents, at least directly, though it may well be that the protecting powers come primarily from them. The single fact that immunity can be brought about by the injection of the bacterial free toxines alone disproves it. There must be other agents, and these have been found to reside within the fluids of the body generally, and hence in the blood serum as it is representative of them all. The normal blood serum free from cells possesses protective powers, for it can be shown to be able unaided to bring bacteria, in certain numbers at any rate, to death and destruction. These powers are capable of being greatly increased.

We have already seen that, if we inject gradually increasing doses of living cultures of a particular bacterium into an animal, we can render it immune to the action of that bacterium. It is, however, usually a partial immunity only, in so far as, although the living bacteria themselves have no effect, their toxines are as powerful as ever. *Vide* Fig. 4. If we inject the latter in sufficient dose the characteristic symptoms of the disease will show themselves exactly as they do in an unprotected animal. If the blood serum, withdrawn from an animal protected in this way, be injected into a second animal, it will confer a similar though generally less strong immunity upon it. Such a serum has in a considerable number of instances the power of inhibiting or paralysing the bacterium and preventing it from producing its toxines. It is called antimicrobic. It cannot actually kill the germs, it can only weaken them so that they fall victims to the normal bactericidal powers of the body. *Vide* Fig. 3. We have already shown that it has usually no antagonistic action to the bacterial toxines, hence we say it is not antitoxic. The antistreptococcic serum (Marmorek), and the anticholera and antityphoid sera (Pfeiffer) are examples of sera, which, although antimicrobic, have little or no antitoxic power. On the other hand, if we produce active immunity in an animal by injecting gradually increasing doses of the bacterial free toxines, we can obtain a serum from it, which will protect another animal from what would otherwise be a lethal dose. Since this serum antagonises the toxines we speak of it as antitoxic. The antidiphtheritic and antitetanic sera are excellent examples. Antitoxic sera always protect against the living organisms also and are therefore antimicrobic, though they may not be bactericidal, for in the instances just given, viz., diphtheria and tetanus, the germs of these diseases grow readily in their respective sera, but they are not capable of producing any result as their toxines are rendered non-effective. *Vide* Fig. 4.

It is the case that in most if not in all infectious diseases, the specific microbe is still present in the individual during convalescence, and often much later, not perhaps in such numbers as during the height of the disease, but still in considerable numbers and in a virulent form. This can easily be demonstrated by cultures or by transference to another animal. They are harmless because their toxines are now neutralised, and after a time they fall victims to the natural bactericidal powers of the tissues and disappear entirely. *Vide* Figs. 3 & 4. The relation and distinction between antimicrobic and antitoxic sera are not always so simple as we have thus sketched. We must for instance guard against thinking that a serum must be purely antimicrobic or purely antitoxic according to the method by which it is prepared. This is true only within general limits, for an antitoxic serum can be obtained by injecting living diphtheria bacilli, as well as by their germ free toxines; and an antimicrobic serum can be obtained by injecting the toxines, freed from their respective germs, *e.g.*, typhoid or cholera, as well as by injecting the germs themselves. The latter is simple enough, but the former is somewhat puzzling and is probably to be explained by the formation of the antitoxic property taking place through the instrumentality of toxines formed by the bacilli within the body.

It is thus seen that certain changes of great moment take place within the blood serum in the establishment of active immunity however brought about, and further that similar changes may be made to occur in a second animal, by transferring into it some of the blood serum of the first. The immunity thus conferred upon the second animal is spoken of as passive or secondary to distinguish it from the active or primary immunity produced in the first animal. *Vide* Fig. 4. Passive immunity of a high degree may often be reached, though it has generally been held to last a relatively shorter time. Recent investigations have tended, however, to throw considerable doubt upon this belief. It has been found that the species of animal employed has a most important bearing upon the result. Thus if we create active immunity in animal **A** and use its blood serum to produce passive immunity in animal **B**, the latter will be practically as powerful and as lasting as the former, provided that both **A** and **B** belong to the same species, *e. g.*, both rabbits; whereas if they be different animals it will be comparatively slight and transient. In other words, an alien serum has little, whereas a friendly serum has much power. Passive immunity forms the basis of serum therapeutics, for since these sera were capable of protecting against subsequent infection, it became natural and far more important to ask if they could also counteract previous infection, and be used not only as prophylactic, but as curative agents. The results have been found to be of a highly encouraging nature in diphtheria and to be not without promise in tetanus, etc.

It is obvious that new and highly complicated problems are thus brought into the question, and generally speaking we may say that the efficacy of any curative serum will depend among other things upon the time of its injection (the earlier the better) and upon the accurate estimation of the dosage. When we think of how these curative sera have been evolved, we may be inclined to say that after all there is some truth in the old saying generally adopted by our homeopathic brethren, "*Similia similibus curantur.*"

A little consideration will show that while a vaccine may have merely a directly or indirectly bactericidal influence a curative serum must have anti-toxic power. In these diseases, *e.g.* typhoid, cholera, etc., in which the microbes invade the tissues and multiply greatly therein, and of which the toxic effects, though always present, are proportionately small in comparison with the numbers of organisms present, the anti-toxic power need not be great, while in others in which the reverse is the case, the anti-toxic power must be much greater. Artificial immunity was obtained in the earlier experiments on animals only after many injections extending over a considerable interval of time, a system inapplicable to man; for, to be useful and practicable, it is obvious that a prophylactic must not require too many injections or take to long a time to act. Later experiments both in animals and man have fortunately demonstrated that artificial immunity even of a high degree can be obtained by very few injections extending over a very short interval of time. In cholera, for instance, it is obtained in four days after two or three injections. In some cases one injection only proves enough, and may be even more efficacious than several. Pfeiffer and Kolle by means of one dose of cholera vaccine in man produced a high degree of protection, as great as that obtained in goats after injections of enormous doses of the vaccine extending over nearly six months. The serum in this case had very great antimicrobic but no anti-toxic power. Pfeiffer recently informed me that he has employed this method with great success in the case of typhoid fever. He finds very large dogs most suitable, and can produce not only a high degree, but the highest obtainable degree of immunity after only one injection. Their serum can protect other animals from lethal doses of the toxines subsequently or even simultaneously introduced. Its effect has not yet been tried upon man. We cannot yet say what interval must elapse between the injection and the production of protective substances. In plague, indeed, it would appear to be very short, about twelve hours or perhaps less, and certainly as soon as the reactionary symptoms following upon the inoculation have disappeared.

It is difficult to understand, much less to explain, how a vaccine can act so quickly. Nay more, in the light of our present knowledge it may seem to us impossible, yet we have the record of experience before us which seems to show that it can actually occur. Future knowledge may unravel the mystery for us. A serum may fail to cure and yet possess considerable antitoxic power. Its failure may be due to its not being strong enough, to its not being administered soon enough, or in sufficient dose, or to yet other causes. Such sera appear to possess strong protective powers which can be quickly brought into play, much more so indeed than is the case with their corresponding vaccines, but when we come to ask why, we can find no answer.

THE NATURE OF THE ANTAGONISM BETWEEN TOXIN AND ANTITOXIN.

The nature of the antagonism between toxin and antitoxin is a very complicated one, and as yet far from being known and understood. Much ingenious speculation and induction has been indulged in, and until very recently we were much at sea regarding it. It has long been closely and keenly debated whether the antagonism was a chemical or physiological one, and the latter view was most generally accepted previous to the publication of Ehrlich's work last year. It led to an earnest revision of the whole question and the balance of evidence and opinion now leans strongly to the other side. Toxin and anti-toxin can be made to combine in a test tube outside the body much in the same way as they do within it, and their various reactions point clearly to the nature of their union being in all probability a chemical one. We can even go further and suggest with much show of reason that their union is similar to that which prevails in the formation of a well known class of chemical substances, viz. double salts. Many of their reactions are in accord with those which regulate the union of an acid and a base, but others do not harmonise with this view, tending rather to support the double salt nature of the process.

Ehrlich suggests that the toxine molecule consists of two atom groups, the one, haptophorous, having the property of binding the toxine and antitoxine together; and the other, toxophorous, carrying all the toxic properties. *Vide* Fig. 5. The former is a relatively simple and stable group, while the latter is complex and unstable, readily breaking down into non-toxic substances which still remain linked to the haptophorous group, thus preserving the integrity of the toxine molecule, now, however, no longer toxic. He proposes the name of toxoids for these non-toxic substances. It is by means of the haptophorous group that the toxine molecule becomes united to the anti-toxine, and hence it will require the same amount of the latter to neutralise it even if it have previously lost all its toxic power. It is possible further that bacteria may sometimes produce, *de novo*, similar toxoid molecules, and not only through the degeneration of a previously toxic group. Ehrlich, indeed, asserts that he has found evidence of this in diphtheria, and proposes the name of toxones for such naturally produced toxoids. We have already explained that when toxines are injected into an animal they lead to the production of anti-toxins within its tissues which may result in their neutralisation. This result will therefore follow whether the toxine molecule preserves its toxic group unchanged or has become degenerated into harmless toxoids.

Should this speculative deduction prove to be well founded it will greatly facilitate the more general adoption of inoculation by vaccines. At present many people object to submit themselves to inoculation, because it means their artificial acquisition of a disease which they might never naturally acquire; and although it produces the disease in a very mild and modified form, yet it at least suggests a certain amount of discomfort, and our luxury loving late nineteenth century bodies dislike present discomfort even with a prospect of future advantage. If, however, toxoid inoculation should prove to be feasible, and if we could thus become assured that the process was perfectly harmless, and, while retaining its full influence for good, was now robbed of all unpleasantness, such scruples to its general adoption would surely disappear.

In further explanation of the production of anti-toxins, Ehrlich supposes that certain cells of the body possess special atom groups which, while normally performing a definite physiological function, have a special affinity for and unite with the toxine molecules when these latter are introduced into the body. *Vide* Fig. 6. This is not entirely speculative, for it has been shown experimentally by several observers that the grey matter of the central nervous system of animals susceptible to tetanus has the power of neutralising a certain amount of tetanus toxine, while in insusceptible animals it has practically no such power. Neutralisation has presumably arisen through combination, and these tissue cells to which the toxine molecules have become linked lose thereby their power of performing their normal physiological function. They proceed to restore it by the formation of new atom groups, which in turn combine with fresh toxine molecules. This process of restoration and fresh linking goes on until there comes a time when the regeneration of these atom groups advances more rapidly than the needs of the cells require either for toxine combination or performance of physiological function. The excess of atom groups is then liberated from the cells and carried into the circulation, where they now act as anti-toxins. It is only after the atom groups have been set free that they can act as anti-toxins. Those still fixed to the cells in combination with the toxines have no such power. It is, indeed, by their means that toxines are able to exert their specific action upon the body. While still circulating in a free condition they are harmless, and if they meet and become linked to anti-toxins, also free, they remain harmless ; whereas, if they become linked to the anti-toxic atom groups when these are still attached to their cells, their toxophorous atom groups can at once affect the cell protoplasm, and their specific action begins to appear. This explanation of the formation of anti-toxins is largely speculative, but there are strong reasons for believing that it is very near the mark. It is a fascinating subject, and we must not now allow it to detain us further.

PRACTICAL LESSONS AND DEDUCTIONS.

It is a reasonable deduction from these facts to say that throughout the whole lifetime of man he is gradually undergoing immunisation of a kind or kinds which will naturally vary with his environment. There are few who do not suffer at times from some minor ailment. It may be but a headache, or indefinite passing malaise, described as being "out of sorts ;" and yet, if we knew all, it might be traceable to a distinct bacterial invasion, the slightness of the results being due perhaps to a fortunate combination of attenuation of the germ and a vigorous state of the resisting powers. Physicians know that many of the infectious diseases may occur in such mild forms, that, although definitely recognisable, they hardly cause any illness, and might not even interfere with the usual routine of the patient's life, were it not that he is a source of danger to others. May they not occur in yet milder forms, and, escaping true recognition, be regarded as simple malaises of a general nature?

There is nothing bacteria loves so much as a virgin soil. Our present great knowledge as to the causation of disease and our greatly improved sanitary methods, have already enabled us largely to guard against infection ; and as we are certain to make still greater progress in this direction, we will be able to do so still more effectually in the future. This very freedom from disease will render us more liable to attack whenever our environment changes. Those of you who have read that clever book by H. G. Wells, called "The war of the Worlds," will remember how the Martians, who had invaded this planet and carried death, destruction, and devastation everywhere, were quickly exterminated by our bacterial forces, although our powers of ordinary warfare had proved powerless against them. If, previous to the invasion, they had only taken the precaution to use some of our protective vaccines, the result might have been widely different. It is a lesson which I hope we ourselves will learn. Not that we intend, so far as I know at any rate, to invade the planet Mars. We have not yet taken from this planet all we want. Our present dominions, as you well know, are widely scattered over every quarter of the globe. Consequently, many of our fellow subjects require to frequently remove their residence from favourable sanitary home surroundings to less favoured regions elsewhere. It becomes us therefore to see that they are protected in every possible way. Preventive inoculation should be employed, especially against such diseases as the plague, cholera, and typhoid fever. The evidence in favour of the protective vaccines from these diseases is now so great as to amply justify their adoption. Pasteurian immunisation has greatly diminished the mortality from natural anthrax among animals. Yellow fever, if Sanarelli's results prove to be true, and yet other diseases are gradually being brought into the protective fold.

The value of protective vaccines in epidemics in this, as well as in other countries, will probably soon be shown to be very great. We cannot expect to meet with equal success in all diseases. In tuberculosis, for example, there are reasons why we should not do so. There is no evidence that one attack protects against a second, and its usual, slow, long-continued and progressive course would seem to suggest that it does not lead to the formation of any protective or antitoxic substances; but experiment has shown that they are really produced, and although success has not yet crowned our efforts, we may at least be said to be "getting warm." Our hopes have been raised several times, only alas to be dashed to the ground again. We had, first, Koch's original tuberculin, then Maragliano's vaccine, and lastly, Koch's new tuberculin R. The first proved valueless and even dangerous (as a curative agent), the second may have secured a certain measure of success in mild cases, but although it may be able to protect against tuberculin, there is no evidence that it can do so against the bacillus itself, or that it can cure affected animals; and the third has been equally unfortunate, having proved so far to have been of little practical value except in a few cases of lupus. Our knowledge of the bacillus of tubercle, of its actions and its products, is now so great, that it is a matter of general wonder that we have made so little progress in lessening its ravages. In one form or other it is responsible for nearly a quarter of all the deaths of this country. There can be little doubt that there is cause here for grave reproach somewhere.

Occasionally the practical sanitarian hurls it at the bacteriologist, crying, "with all your discoveries what good have you done?" This is doubtless but the bitter wail of the practical man driven to despair, for the bacteriologist might well retaliate and ask if full use had been made of the discoveries he had already provided. If steps had been taken, for only a few years back, to secure the destruction and prevent the dissemination of the bacillus, especially in the crowded houses of the poor throughout the land, there is every reason to believe that the mortality, which we have still to-day to deplore, would have been enormously diminished. The public conscience has been awakened at last, and the mighty voice of the people hath spoken, so that we may look confidently forward to great practical good coming from the present day crusade against tuberculosis. It will be well if Birmingham is found in the van of this clamant and much needed reform, as she has so often been in other great and noble efforts.

EXTENSION TO DIAGNOSIS.

The principles underlying protective inoculation have within the last few years received practical application in yet another direction, and have given us a new method of diagnosis of great value, which is generally spoken of as "the serum method of diagnosis." It has been demonstrated by an elaborate series of investigations that the serum of an immune animal, when added to an emulsion of a young culture of the various motile organisms, *e.g.*, cholera, typhoid, causes the germs to gradually lose their power of motion, and to become gathered together into clumps. It is a specific and not a general reaction, a typhoid serum acting only on the typhoid bacillus, a cholera serum upon the cholera bacillus and so on. So complete and extensive is the reaction that it can be seen, not only by the aid of the microscope when small quantities of the fluids are mixed together upon a slide, but also by the unaided eye when equal parts of diluted typhoid serum and bacterial emulsion are placed together in a thin glass tube. This mixture, instead of remaining uniformly morbid, becomes gradually clear, so that after the lapse of about twenty-four hours, the upper part is quite clear, whilst the lowest part is occupied by a dense precipitate consisting of motionless bacilli agglutinated together in clumps. The latter is known as the sectimentation test. It may form a useful control to the microscopic method.

It was already known that the serum from a convalescent typhoid patient could confer upon animals a certain amount of protection from typhoid, and Widal further found that it could produce this clumping reaction. He then discovered that it was not necessary to wait for convalesence, that the reaction was given at a very early stage of the disease, generally appearing as early as the seventh day and sometimes considerably earlier. It could therefore be used as a means of diagnosis. It gradually becomes more marked as the disease advances and is generally well marked though occasionally it disappears during convalesence. It may still be present after several months, but we cannot yet say how long it usually lasts. Pericardial and pleural effusions, the bile, the milk, and to a less degree the urine from cases of typhoid fever also give the reaction. In cases where the serum of the mother gives it distinctly, that of the fœtus may or may not do so. The circumstances determining the passage of the agglutinines through the placenta have not yet been determined. The normal serum of the horse, the ass and the rabbit will clump not only the typhoid bacillus but the coli as well.

Many other important particulars regarding the reaction might be given, but they concern the true nature of agglutination, about which we are still much in the dark, rather than its value as a practical means of diagnosis. An immense number of observations have now been made as to the latter, and there appears to be no doubt that it is thoroughly reliable, and will give an accurate result, if due precautions be observed, in nearly 95 per cent of all cases. It is then not only a valuable aid to diagnosis, but it may give earlier and truer indications than the clinician can obtain by means of his whole armamentarium. It is applicable to other diseases caused by other motile organisms, *e.g.*, bacillus cholera, bacillus coli, plague, &c., and some at any rate of the non-motile forms, *e.g.* bacillus of glanders. Whether the changes which bring about this clumping action are connected with the production of immunity or not we cannot say, but it would at any rate appear to be certain that very early in the course of certain diseases the blood serum acquires properties which exert a paralysing action upon the causal bacilli. They are not killed for they can still manifest their specifie action. A precisely similar action is exerted by most antimicrobic sera. Of themselves, they have no power to destroy, but only to inhibit their specific bacilli, which are killed only when the bactericidal powers of the body come into play. So here, if a solution containing clumped bacilli be injected into the peritoneal cavity of a healthy animal, or even added to some of its peritoneal fluid in a test tube, the bacilli will become disintegrated and disappear in the fluid.

The foregoing propositions embody the principles which govern the whole range of the science, but there are others which apply more particularly to individual organisms, and it will be necessary to refer shortly to them.

The pyogenic group.—Among the pyogenic bacteria much has been done towards the elucidation of the precise role played by some of the less known forms such as the micrococcus tetragenus, towards the resolution of the varieties of the streptococcus, towards determining the action of the bacillus coli, and towards settling the pus producing power of the typhoid bacillus. The systematic examination of every purulent fluid would do much to clear up these and kindred questions. Film preparations should be made in all cases and cultures in most. The clumping re-action test should be applied in all purulent fluids where typhoid is or has been present or suspected.

The gonococcus.—In few diseases will a systematic examination of the discharge by means of films so well repay the practitioner as it does in gonorrhœa. If the dried films show large numbers of micrococci having the peculiar characters, position and staining re-actions of the gonococcus, we may confidently assert that the disease is gonorrhœa; and further, we can in the acute stage at any rate, thus make a positive diagnosis earlier than by any other method. Some authorities even hold that we may thus also gain much information as to the prognosis, but, be this as it may, there is no doubt that the systematic and periodic examination of the discharge by means of films in every case is of great value.

The pneumococcus.—The pneumococcus is the cause of acute pneumonia, though it may be associated in some instances with pyogenic organisms. It is plentifully present in the sputum and lungs both before and after the crisis of a non-fatal case, though less numerous at the latter time; and when we consider that in fatal cases death rarely follows from interference with the function of the lungs, but from cardiac failure, or hyperpyrexia, or general nervous depression, we are led to conclude that the general effects are caused by toxines, which become balanced and overcome by antitoxins naturally produced within the body by the time the crisis has been reached. This line of thought has stimulated work aiming at the preparation of both a preventive vaccine and a curative serum. Although we have so far failed in the latter we have succeeded in the former quest, and it is a step in the right direction.

The tubercle bacillus.—If tubercle bacilli in any numbers be found in the sputum of any case, however uncertain or slight the clinical signs may be, we may with confidence assert that there is tubercular disease of some part of the respiratory tract, generally the lungs. The fact that they are occasionally found in small numbers in the sputum of a non-tubercular case which has been for a time in close proximity to a tubercular one can easily be eliminated. It is of no practical importance beyond teaching us the necessity of separating such cases. Tuberculosis has undoubtedly been thus acquired in the past and it is our bounden duty to prevent its recurrence in the future.

Similarly the presence of tubercle bacilli in the urine or effusion from the pleura or other serous cavity is indubitably diagnostic of the true nature of the case. We may discover tuberculosis by other means, the most important of which is the use of tuberculin in cattle. Thirty to forty centigrammes are injected, and if the temperature rises 2 to 3° F. in 8 to 12 hours, and continues up for 10 to 12 hours, we may safely conclude that the animal is tubercular. If the method be carried out properly it will be found to be fairly free from error. It fails in about three per cent. of the cases. It is being largely carried out on the continent, and to a certain extent, though not yet nearly widely enough, in this country.

Glanders.—Mallein can be used in the same way to diagnose glanders in animals, and veterinary authorities are practically unanimous that the test is one of great value.

Anthrax.—A recent act makes it illegal to open the carcase of an animal suspected to have died of anthrax, and veterinary examiners are sometimes at a loss how to proceed to obtain an irrefutable diagnosis. It is best to open one of the auricular veins and make both films and cultures from the blood. In man the same two steps are taken, using a little of the fluid from the vesicles or from a scraping of the incised or excised pustule.

Diphtheria.—There is no better instance than diphtheria in the wide range of diseased conditions, of the great assistance which Bacteriology has rendered to both the Science and the Practice of Medicine. Not only does it provide them with the only true, efficient, and reliable means of diagnosis, but it explains how the various phenomena characteristic of the disease are produced, and affords the best means of treatment yet discovered.

The true scientist is the least mentally prejudiced of men; and while perseveringly striving with singleness of heart and purpose for the discovery of truth, and to further the health and welfare of mankind, he is ever ready to acknowledge the help and recognition given to him by others; and it is therefore a source of great pleasure and satisfaction to the Bacteriologist to be able to put on record the ready and full assistance a generous recognition of his efforts towards the checking of this disease have received at the hands alike of his professional brethren, the practical physician and medical officer of health, and his lay brethren, those who hold place on the health board of cities. I have already seen enough in my work here to be able to say that no city is deserving of greater honour than Birmingham and some of her neighbours in this respect, and I hope soon to be able to include every town and district in the midlands in this mede of praise. The new worker in the bacteriological laboratory of this College finds ready to his hand a system so good, a practice so thorough in relation to the diagnosis of this disease, carried out too, be it remembered, under difficulties that none but the initiated can rightly appreciate, that he is perforce constrained to congratulate medical and lay authorities alike on what they have already done, and on what with the increased facilities now provided, they are likely to be able to do in the future. I cherish the hope that the department over which I preside will furnish a place where the skilled proficient in this or any other disease, or the aspirant thereto, will find a hearty welcome, and every facility placed within his reach to help and to stimulate him in his search after knowledge. We need not in our present theme do more than refer in outline to the immense services which bacteriology has rendered to medicine in relation to diphtheria.

Clinicians in the past were wont to determine the presence or absence of this disease largely from the appearance and site of the membrane. Distinctions so drawn are now known to be of no value whatever, and I hope it is generally accepted and understood, as it is undoubtedly true, that a case may present all the old classical signs of diphtheria, so far as the appearance and distribution of the membrane is concerned, and yet be not diphtheria at all: and *vice versa*, a case may present none of these signs and yet be true diphtheria. I do not wish to appear in any way to exaggerate or to shake the confidence of the clinician in his powers of diagnosis, yet I say without fear of contradiction, that the only true and irrefutable means of determining whether a case is one of diphtheria or not lies in finding the bacillus in the throat. It is unnecessary to dwell here upon the difficulties which the bacteriologist may encounter in deciding upon the specific nature of the bacillus met with in any individual case, as to whether it is the true diphtheria bacillus or one of the forms which closely resemble it, but yet possess far less power and importance. Suffice it to say that they are such as melt away before the exhibition of his skill, and that with the tests as to staining, growth, and anatomical appearances at his command he is able to return an unhesitating answer. It may be urged that he is unable to exclude the pseudo-diphtheritic bacillus from his calculations, and it may be as well to give a clear pronouncement upon this point. That there are bacilli which closely resemble the diphtheria bacillus in nearly every aspect, and yet are not the same, need not be denied; but the sooner it is generally accepted that all bacilli which agree in the characters mentioned above, when tested by the skilled observer, are indubitably diphtheria bacilli, the better for diagnosis, prevention, and treatment. It is no proof to the contrary that a bacillus while conforming to our tests is yet non-virulent. Every bacteriologist has found how quickly and frequently certain of his cultures of undoubted diphtheria bacilli lose all toxic power. Such bacilli are frequently found in the throats of healthy individuals. They may, under circumstances yet unknown to us, become virulent, and be the *fons et origo* of many an outbreak of the disease which so far has remained a mystery to us.

Tetanus.—The clinical symptoms of this disease are generally so conclusive of themselves that the practical observer does not feel the same necessity for bacterial corroboration; yet it ought to be carried out in all cases. The wound, and it ought to be clearly and decidedly proclaimed that a wound or abrasion of some soit must be present, should be examined for the bacillus by means of film preparations of the discharge. Cultivation and inoculation may have to be used before a decision can be given, but one or other usually affords conclusive proof. The popular belief that a wound of the hand or foot is particularly dangerous in its liability to be followed by lockjaw has no more foundation in fact than that in such positions it is more liable to be contaminated by dirt than in others. The bacillus is one which flourishes in the soil, and every wound which shows signs of contamination by soil, especially if ragged and unhealthy looking as well, ought to be examined bacteriologically. The presence of tetanus may thus be detected before any symptoms appear, and the earlier application of the proper treatment may achieve more successful results than we have hitherto been able to obtain.

Cholera.—This is not a disease of which we are likely to have much practical experience in this school of medicine, yet it is a disease to which many of our fellow subjects of this Great British Empire are exposed, and hence we, like other teachers of young practitioners, who may be called upon to practice all over the world, must be prepared to deal with it. It is another striking instance of the contributions which bacteriology has made to practical medicine. Alike in diagnosis and treatment it has provided the most effectual means of dealing with the disease. A microscopic examination of the dejecta is frequently sufficient, as many cases give almost the appearances of a pure culture. Koch states that during the Hamburg epidemic this method was sufficient in 50 per cent. of the cases. In other instances other methods known to bacteriologists, including the serum method, must be practised, and one or other is certain to meet with success.

Influenza.—This has become quite a fashionable disease. So prevalent has it really been and often so serious in its consequences that the sufferer readily secures the sympathy of his friends. This leads him to hope rather than otherwise, when his illness even remotely resembles influenza, that this will be the fiat of his doctor, and there can be little doubt that medical men, always ready and willing to further their patient's wishes, have greatly increased the elasticity of their diagnosis of this disease. The patient indeed is rather proud of being its victim. It is quite common for him to declare to his friends, that his own opinion is that a particular ailment from which he has just recovered really was influenza, although his doctor, not detecting it, thought it to be something else. Usually, the doctor is only too ready to humour his patient, so that the scrupulous and conscientious part of the lay mind has begun to be a little sceptical on the subject. The great frequency and chameleon like aspect of the disease have already caused not a little misgiving. Regretful doubt keeps whispering that the physician may be wrong. Here is a chance for the bacteriologist. His methods cannot err. His films and cultures made from the small round masses of greenish yellow sputum are beyond all doubt. Think of the pride of the man and woman who, with a bacteriologist's certificate in their pockets, may claim their place among the *élite* without fear of question or cavil.

These diseases which I have thus specially mentioned are fair representatives of the whole, and I need not detain you with references to others. Long and laborious study is needed to attain even a moderate proficiency as a bacteriologist, and no man can well become a past master in every part of the science. Marmorek, who has devoted more time than any other worker to the streptococcus alone, when asked how long it would take to master this one organism thoroughly, answered that he did not know, for he had worked at it for only eight years. He is still a young man, and perhaps he may yet have an opportunity of answering this question in the words of the great Torwaldsen, who when asked how long it would take to know The Eternal City thoroughly, answered that he did not know, for he had only lived there for forty years.

I am well aware that this endeavour to place before you the recent advancements and refinements, which bacteriology has accomplished in the domains of the diagnosis and prevention of disease, labours under all the imperfections and disadvantages, which usually pertain to any attempt to explain a difficult and complicated subject within limited and popular lines; but I have remembered that however great the interest and fascination, which the elaborated experiments, arguments and discussions, that go to the establishment of all great doctrines, have for the specialist, they cannot be expected to appeal in the same way to others, particularly to the already overtaxed and over-burdened practitioner and student of medicine. I am sure you will thank me, inwardly at any rate, for having mercifully spared you their infliction. I hope, however, that I have said enough to demonstrate the immense value of the assistance, which the bacteriologist is able to render to mankind, both in diagnosing and preventing disease. I do not wish it for one moment to be supposed that I think his methods can, in any way, supplant those of the clinician. They are but the complements thereof. Let him continue to exercise his clinical skill as fully, as freely, and as perfectly as of old; but let him accept the bacteriologist as an honourable helpmate, and never hesitate to call to his aid the assistance which he so abundantly provides, and is always pleased to render. It is by working loyally side by side and hand in hand that the clinician and bacteriologist can best carry on the struggle against disease. Let them continue at all times to strive together for the health and welfare of mankind. Without health, enjoyment in life is indeed hard to find. With it, we have a pleasure in listening to the teachings, and striving to follow the precepts of the Platos and Priestleys, the Gairdners and Muirheads of this world *Sanitas est vita*, and "without the means of life our lightest ideal hangs idle in the air." Let the clinician and the bacteriologist work together to secure for mankind such a life of health as will enable him to fully devote himself to the ideals and pursuits, which satisfy and beautify his life, and thus secure for him the opportunity of keeping his cup of happiness not only full to the brim, but running over.

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