thing of the kind should occur the doctor will deal with them at their onset, and will often prevent them from becoming serious. The idiosyncracies and peculiarities of each case also are noted and treated separately; there is no mere routine treatment, and it is often possible to take the patient into our confidence, and to make him work with us for his cure. All this is impossible in ordinary general practice, but it is carried out in most sanatoria. Lastly, every patient is taught how to regulate his cough, and how to prevent danger to others in the disposal of his sputum.

POSSIBLE OBJECTIONS TO SANATORIA FOR CONSUMPTIVES.

It has been made a serious reproach to all forms of hospitals or other establishments for phthisical persons that they are likely to become centres of infection, and that the disease will thus spread from the sick to the healthy. This accusation has, however, been amply disproved for most of the hospitals for consumption in this country.

It has been shown that there has been no such spreading of the disease even in the large hospitals in London and Manchester; and if this is the case in these great towns, it is still less likely to occur in the breezy open-air treatment of phthisis.

I have myself been able to prove that the most virulent tuberculous sputum entirely loses its power of conveying the disease after a comparatively short exposure to fresh air and sunlight; an exposure, in fact, too short to have permitted the formation of the fine tuberculous dust in the air which is the most potent means of contagion.

In sanatoria, where the air is freely flowing through the rooms night and day, and where there is full exposure of every dormitory to the light of the sun, we may be quite sure that the possibility of this accident is reduced to a minimum; and we may add that the care that is taken to disinfect and destroy every particle of sputum is sufficient to make infection from the patients an impossibility.

Another objection of more importance is that the patients are exposed to all the depressing influence of the presence of many invalids in all stages of the disease, and that the want of amusement and distraction is apt to cause *ennui*.

It must be admitted that to healthy people the sight of so many poor sufferers collected within the comparatively narrow limits of a sanatorium is a sad one; and it is no small tribute to the ability of most of the chief medical directors of these establishments that they have been able to triumph over the many depressing conditions that must prevail in them, and that they have succeeded in infusing a spirit of content and hope into the minds of most, if not all, of their inmates.

It must, however be remembered that these persons are all seeking a cure; that after a short stay in the place the amelioration of their condition becomes so manifest that they are ready to rejoice and to compare notes with other patients. Their life also is so taken up with the continual attention and care of the nurses and doctor that they have little time in which to nurse their sorrow, or to express their compassion for others.

I have visited several of these places on the Continent, and can testify to the general air of cheerfulness and hope which characterised the patients; moreover, the doctor in attendance was always able to assure me that the life was by no means a dull or uninteresting one, and that the tranquil amusements and little indulgences that were allowed amply sufficed to satisfy the most impatient of the invalids.

The truth is that the extraordinary success of this method of treatment, and the daily watching the progress towards cure of so many who otherwise must have been regarded as desperate—this daily spectacle, and the constant attention of the attendants, make the life of a sanatorium far from being the sad and lugubrious thing that we might imagine it to be.

Another important point is the question of cost. It may well be regarded as certain that it is impossible to bring together all the appliances of a sanatorium and to supply the inmates with the luxuries that they absolutely need without a considerable expenditure.

REFERENCES.

¹ *Parkes's Hygiene*, edition vi, p. 135. ² *Proc. Roy. Soc.*, vol. lvi. ³ *Diseases of Lung*, p. 385.

THE CROONIAN LECTURES

ON THE

CHEMICAL PRODUCTS OF PATHOGENIC BACTERIA CONSIDERED WITH SPECIAL REFERENCE TO ENTERIC FEVER.

Delivered before the Royal College of Physicians of London,

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LECTURE IV.

THE ACTION OF THE POISONS OF THE TYPHOID BACILLUS, GÄRTNER'S BACILLUS, AND THE BACILLUS COLI COMPARED WITH THAT OF OTHER ALLIED POISONS.

THERE are two poisons which are not the products of bacterial action being found in the seeds of plants, and which are of great interest in connection with the toxic products of the three bacilli which have been examined. These poisons are ricin, obtained from the seeds of the castor-oil plant, and abrin, obtained from the seeds of the abrus precatorius. The latter is used in India in the poisoning of cattle, and its symptoms are those of a general toxæmia. Both these poisons produce conjunctivitis when applied to the eye, and injected under the skin they cause diarrhoea with great general prostration. In an investigation I conducted some years ago I found that the two proteids present in the seeds of the abrin—namely, a globulin and an albumose—were both poisonous, and that they both produced similar symptoms. In one experiment a pigeon, weighing 216 g., received 0.2 g. of abrus globulin, and death followed in six hours, and was preceded by an increase in the number of respirations and a great lowering of the temperature, the total fall being 23.8° F. or 12.6° C. In another experiment a pigeon weighing 355 g. received 0.02 g. of the abrus albumose. The symptoms began in four hours and a half, and the animal died in about six hours. There was a more or less continuous fall of temperature, and, unlike the first animal, the number of respirations per minute fell instead of rose. In the rabbit abrin produces, like the poison of the typhoid bacillus, a rapid fall of temperature and death. The fact that the abrus proteids produce diarrhoea, which is most commonly bloody, is remarkable. This is associated with the signs of a hæmorrhagic gastro-enteritis, there being great inflammation of the mucous membrane of the intestine, and especially of the adenoid patches. The abrus poisons are very sensitive to heat, the action of the globulin being completely destroyed by the momentary raising of temperature of its solution to 75° or 80° C., that of the albumose at a rather higher temperature, 85° C. What property it is of the proteid which has this toxic action, whether it resides in the proteid itself, or whether there is some toxic body, possibly of a ferment nature, attached to the proteids, it is impossible to say; but the similarity of their action to that of the toxic products obtained from the closely allied micro-organisms, the typhoid bacillus, the Gärtner's bacillus, and the bacillus coli is remarkable. No doubt in all these cases the effect on the intestine occurs during the excretion of the poison by the mucous membrane in whatever way it may be introduced into the body. The diphtheria poison sometimes produces diarrhoea when given in sufficiently large doses, a result which I never obtained from the injection of even large doses of the albumoses of anthrax or of ulcerative endocarditis, and this is also not an effect which is noticed as a result of the action of the tetanus poison.

With regard to the diphtheria poison, the effect on the temperature and on the body condition of different doses is seen in the following experiment. A mixture of the albumoses and toxin was used, and in the first experiment 2 c.cm. were injected into the marginal vein. This was followed by some rise of temperature on the same day, and on the next day weakness in the hind legs appeared, and a rapid fall of temperature to about 96° F. occurred, ending in the death of the animal. In another experiment when 5 c.cm. of the same poison was given there was a great rise of tempera-

ture, and the animal died during the night. Neither animal showed any diarrhoea or intestinal symptoms, and the general effects were in marked contrast to the effects of the poisons in the three bacilli investigated.

The effect of the diphtheria poison in reducing the temperature of the body is also shown in another experiment in which a mixture of the albumoses and secretion of the bacillus, which had been dried, was given. Altogether 0.2 g. of this powder was injected into the marginal vein. After the first injection there was scarcely any rise of the body temperature, but the next morning the temperature had fallen 3°, and a second injection of a small dose still further increased the depression of temperature, the animal dying in twenty-four hours. The fact, therefore, of a bacterial poison reducing the body temperature is not limited to the three bacilli which we have investigated, although it is a prominent feature of the action of their products. The diphtheria poison is readily affected by heat; thus, in one experiment it was seen that after heating to about 60° for one hour, the injection of 5 c.cm. solution of toxin produced, not a rise, but a fall of temperature, and this was followed by a slight reactionary rise to the normal, after which the animal recovered and showed no symptoms. In another experiment, however, 5 c.cm. of diphtheria toxin, heated for ten minutes at 60° C., produced a continuous but gradual fall of temperature up to the time of death on the fifth day of the experiment.

Comparing this with a similar experiment in which the same dose (unheated) was given to another animal of the same weight, it was seen that the temperature rose somewhat after the injection, and that the animal died the following night. The heat had, therefore, weakened the action of the toxin, and this weakened toxin, instead of producing a rise of temperature, produced a continuous fall, an interesting result when compared with the effects of the products of the three bacilli. It may be concluded that a small dose of the toxin or a weakened toxin may produce a fall of temperature and no other change, and that a larger dose of the toxin may produce a rise of temperature, followed by a fall which precedes death, or it may in some cases be recovered from; and that a large dose of the poison may also produce a sudden and rapid fall of the body temperature, ending fatally in a few hours.

The effect of the diphtheria poison in producing a palsy dependent on degeneration of the peripheral nerves, and that of the tetanus poison in producing convulsions, is in marked contrast to that of the products obtained from the three bacilli, inasmuch as there was no evidence of palsy in any of the animals, even if they lived three weeks or longer, and no evidence of any convulsions. There was no nerve degeneration. The effect of the abrus poisons on the respirations is well marked, producing in some cases, as has been shown—a rise in the number of respirations, and sometimes a fall even, though in both cases the temperature persistently falls. The diphtheria toxin also has a profound effect on the respiratory system. A monkey weighing 1,575 g. received intravenously on successive days two doses of diphtheria albumoses, each of 0.3 g. After the first injection there was a depression of the rectal temperature, followed by a rise to a little above the normal, and afterwards, as well as following the secondary injection the temperature became irregular, although not very high; until the end of the ninth day of the experiment, after which it was normal. The respiratory curve showed, however, a greater irregularity. After the first injection there was a rapid rise in the number of respirations until they were nearly 80 a minute. Afterwards they fell, but following the second injection there was a gradual rise, and the respiratory curve remained irregular until about the ninth day, when it fell to about 40 a minute. The effect of the injection of this poison on the general condition of the body was remarkable. After the first dose there were no general symptoms, but in three hours after the second dose the animal became progressively weaker, so that in seven hours it could not sit up or move the arms and legs. There was complete motor palsy of the limb and trunk muscles, but no respiratory paralysis and no palsy of the facial muscles, as the animal lying on one side, with food within reach of its mouth, ate vigorously and swallowed perfectly. No knee-jerks were obtainable, and no reflex on pinching the limbs. This condition lasted for over twenty-four hours after the second injection, and in twenty-six hours

the animal could sit up, but there were still no knee-jerks. These reappeared on the second day following the injection, and recovery from the motor and sensory palsy was complete about the same day. The animal gradually and completely recovered and remained quite normal for several months, when it was killed. It may be remarked that the features of the palsy were those of a complete suspension of the functions of the spinal cord.

Like the diphtheria toxin, tetanus toxin acts on the spinal cord, but in another direction—it produces convulsions instead of paralysis, and it produces this effect not only in the higher animals, but in rodents. The diphtheria toxin does not affect the spinal cord in rodents; it produces a well-marked and universal degeneration of the peripheral nerves in the manner I have elsewhere described. The tetanus poison also, to some extent, acts on the peripheral nerves, inasmuch as I have found in animals which have received a small dose of the poison, and which have survived for some time, distinct degeneration in a few branches of the anterior crural nerve and in the phrenic. The degeneration is, however, extremely slight, and is not sufficient to cause signs of paralysis during life. A special action on the cerebral hemispheres is to be ascribed to the anthrax products, and especially the alkaloidal body, inasmuch as they produce stupor ending in coma, which may either be recovered from, or, as is more usual, end in death.

ACTION ON THE HEART MUSCLE.

In previous papers I have shown that it is a characteristic of the action of the albumoses of anthrax and of ulcerative endocarditis, as well as of the diphtheria poisons, to produce a well-marked fatty degeneration of the cardiac muscle, and this is as marked in the case of the anthrax albumoses as it is in the case of diphtheria poison. The poison of the typhoid bacillus produces the same result, although not to such a marked extent. In those animals which died slowly some change in the heart muscle was almost constantly observed; sometimes, however, it was absent. In none of these animals was any degeneration of the peripheral nerves discovered, though branches of the anterior crural and phrenic nerves were frequently examined after staining in osmic acid. The actions of these poisons on the heart is therefore one independent of any action on the nervous system, and is probably a direct toxic effect on the cardiac muscle. All the bacterial poisons which I have myself examined produce a profound change in the general nutrition, which is in many instances independent of any fever produced, and it may be that the degeneration of the heart muscle is only an expression of this disordered nutrition. Degeneration in the skeletal muscles, however, is not found. The structural changes which occur in the organs are the result of the action of these poisons, a subject which has been worked out very fully by Dr. Simon Flexner.¹

CHEMICAL NATURE OF BACTERIAL POISONS.

I have previously said that very little is known of the chemical nature of the poisons we have been discussing. There are three theories which have been discussed in regard to them: (1) as to whether the poisons are albuminous substances; (2) whether they are of a ferment nature; (3) whether they are crystalline chemical substances, or at any rate not proteid, although they may in some way be associated with the proteid.

Poisons of Proteid Nature.—Some of these poisons are so closely associated with proteids as to be inseparable. There is, for example, no question whatever that the albumoses of gastric digestion are poisonous when injected into the veins of an animal, and so also are the albumoses formed by the bacillus of anthrax, and that the poisonous nature of these substances is somewhat, although not greatly, diminished by heat. The poisons, however, which have given the greatest difficulty in the discussion as to whether they are of a proteid or of a ferment nature are those of abrus, ricin, and snake poison. The abrus seeds, for example, contain a globulin and an albumose, both of which are poisonous, and if the globulin be precipitated from its solution by heat its toxicity is lost, and if the albumose is heated to a temperature of 85° C. its toxicity is also completely lost. In this case it may with plausibility be argued that inasmuch as the toxicity of both the bodies is destroyed at nearly the same temperature, it is

not the proteid itself which is poisonous, but something associated with the proteid, that is, some body of a ferment nature. The same difficulty exists with the question of snake poison. Generally speaking, in the venom of the viperine snakes there are two proteid bodies—a globulin and an albumose—both of which are poisonous, and each of which appears to have a distinct action, the globulin acting more particularly on the blood, the albumose acting more particularly on the nervous system (C. J. Martin). If the globulin be precipitated from its solution by heating it to its temperature of coagulation its activity is destroyed, but the toxic properties of the albumose are still intact. Cobra venom does not contain so much globulin as that of the viperine snakes, so that heating its solution to the temperature at which the globulin is coagulated does not greatly diminish the toxicity of the venom, and it requires the solution to be boiled for a short time before the poisonous action is destroyed. From these facts it certainly appears that the toxic action of snake venom is so closely associated with the proteid as to be inseparable from it, and that there is something in the constitution of the proteid molecule—whatever that may be—which confers this great poisonous property on the venom.

Poisons of a Ferment Nature.—Several considerations, however, prevent the conclusion that all these poisons, including the bacterial, are of a proteid nature. Diphtheria poison, for example, is practically as toxic as cobra venom, or as the venom of the Australian black snake (*hoplocephalus curtus*). As previously stated, Roux and Yersin obtained the product from the broth solution in such a form that it acted in imponderable doses. Since that time Brieger and Cohn, by means of the precipitation by zinc salts, and the subsequent decomposition of the zinc salt with carbonic acid, obtained a toxic product from diphtheria, causing all the characteristic symptoms, but not giving any proteid reactions, neither the xanthoproteic nor the biuret reaction. It may be considered, therefore, that the diphtheria poison is not necessarily associated with a distinct proteid. It may be that this poison, together with the poison of tetanus and that which we have discussed as formed by the typhoid bacillus is of a ferment nature. The arguments which may be used in this respect are: (1) That they act in infinitesimal doses; (2) that they may act slowly and produce death after many days by profoundly affecting the general nutrition; (3) that they are sensitive to the action of heat in a way that no chemical poisons are known to be. If, of course, these poisons are of a ferment nature, their physiological action is unlike that of any of the other known ferments. They are not digestive ferments in the ordinary sense of the word. I have performed several experiments to test the digestive action on ordinary proteids of the diphtheria and tetanus poisons, and have never obtained the slightest indication of digestion. If they are considered as ferments they must be substances which have a peculiar affinity for certain tissues of the body on which they produce their special toxic effect. Thus, the diphtheria poison selects the peripheral nerves for one of its chief actions, and in some cases the spinal cord. The tetanus toxin produces its most marked effects on the cells of the spinal cord. Abrus, ricin, and the poisons of the three bacilli we have examined produce a pronounced effect on the body temperature, besides which they have a marked action on the small intestine. They produce no special effect on the nervous system, except perhaps in the case of abrus and ricin, which appear to affect the respiratory centre in the medulla. In each case, therefore, the ferment—if ferment it be—must be essentially different, for although they may have a similarity in action yet their differences are considerable, and especially is this so in considering the results of the toxic reaction of these poisons in the body—the most delicate test for the identity of these poisons. Thus, in the case of abrus and ricin, the actions of the poison are closely similar, ricin perhaps acting rather more vigorously than abrus, so that—so far as their physiological action goes—if that alone were investigated they might be considered as identical substances. But Ehrlich found that an animal which had been made immune to abrus was not immune to ricin, and *vice versa*. Similarly, the diphtheria antitoxin does not counteract the effects of the tetanus poison, nor does the tetanus antitoxin protect against the diphtheria poison.

The association of digestive products with these poisons is an interesting one; in snake venom and in abrus albumoses are

present, and these are also formed by the micro-organisms that we have been discussing. The amount of digestion, however, which each individual bacterium produces varies considerably, being greatest with the bacillus of anthrax, and least with the typhoid bacillus. These products of digestion are formed either by the bacillus ingesting the proteid and discharging it as albumose, or the digestion occurs by means of a proteolytic ferment secreted by the bacillus in the body of an individual or animal suffering from the disease.

It may be interesting to add the following table² of the comparative toxicity of these substances. The figures in the column represent the number of grammes of body weight of a rabbit which will be killed by 1 g. of dried poison:

Cobra venom	...	...	...	...	4,000,000
Hoplocephalus curtus	...	...	...	...	4,000,000
Diphtheria toxin...	...	...	...	...	4,000,000
Ricin	...	...	...	...	1,500,000
Pseudechis	...	...	...	800,000 to	2,000,000
Pelias berus	...	...	...	...	250,000
Anthrax albumoses	...	...	...	...	3,000
Cholera albumoses	...	...	...	...	3,000

THE RELATION OF THE TYPHOID BACILLUS TO ENTERIC FEVER.

The relation of the typhoid bacillus to enteric fever has been much discussed, and some confusion has been caused on the subject by work which was done some years ago with non-virulent or slightly virulent forms of the bacillus. It is constantly present in cases of typhoid fever in the intestinal lesions, in the spleen, the mesenteric glands, and sometimes in the blood. It is in not a few cases found in the urine; it is also found, though not constantly, in the faeces. The constant presence of this pathogenic organism in the lesions of the disease is one of the arguments in favour of its being the cause of the condition, and in most cases, as we have seen, it may be obtained in pure culture from the spleen after death. The second argument in favour of the bacillus being the cause of enteric fever rests on the sedimenting reaction, and Widal's reaction, which is given by the blood serum of typhoid patients in certain dilutions, causing the bacilli from a young culture to become motionless and to clump together, and sinking to the bottom of the vessel in which they are contained. This reaction is specific; it is not given by the bacillus coli, but, according to Dr. Durham, it is given to some extent by the bacillus of Gärtner.

A similar reaction was obtained from the blood serum of animals which have been rendered artificially immune to the typhoid bacillus. We must consider, therefore, that the serum reaction given by typhoid patients is due to the effects of the typhoid bacillus which is present in their bodies. It is a noteworthy fact that normal rabbit serum gives a clumping reaction with the bacillus coli, and that the serum reaction with the bacillus coli, when artificially-prepared coli serum is used, is, according to Dr. Durham, very variable. Typhoid serum never gives a reaction with the bacillus coli, nor does the coli serum give a reaction with the typhoid bacillus. This constitutes an important difference between the micro-organisms. The difficulty with regard to the question of the typhoid bacillus rests mainly (1) on the fact that this disease does not exist in the natural condition in any animal but man. In man it is a very characteristic disease, with definite intestinal lesions and a definite enlargement of the mesenteric lymphatic glands and the spleen. (2) Another statement which has been made is that the typhoid bacillus is not infective. With regard to the first point, enteric fever is in the same position as any of the other diseases which affect man alone, and the difficulty is removed if it can be shown that the typhoid bacillus reproduces the same lesions as occur in the human being. Many attempts have been made to infect animals by way of the alimentary canal with the typhoid bacillus, and most of them have been unsuccessful. The want of success does not appear to depend solely on the fact that non-virulent bacilli have been used, but also on the fact that animals are extremely insusceptible to infection through the alimentary tract by the typhoid bacillus. In my experiments I gave to two rabbits enormous and daily doses of the virulent bacillus, with the production of no result beyond fever in one animal lasting one day. Dr. Remlinger³ appears to have been more successful, and to have produced in some rabbits a definite

infection by giving them virulent cultures with their food. Some rabbits were unaffected; others, after a period of fever, diarrhoea, and bodily depression with loss of weight, underwent complete recovery. Others, again, were affected in the same way and succumbed.

At the *post-mortem* examination there was great congestion of the small intestine, which contained liquid matter. Peyer's patches were enlarged, and there was some ulceration at the level of the cæcum. The spleen was greatly enlarged, and the bacillus was obtained in a pure culture from the organs. In one experiment the animal was fed for five days with the typhoid bacillus; on the eighth day fever was observed, and there was the train of symptoms which had been mentioned up to seventeen days when the animal was dying. In another experiment seven days after feeding the fever began, and the symptoms progressed for twenty days, when the animal died. Similar results were obtained in rats. One important point is noted by Remlinger, namely, that the blood serum of the animal infected gave an agglutinating or sedimenting reaction. There can be no question from these experiments that an infection of the animal by way of the alimentary tract was produced, and that the chief stress of the disease was on the small intestine. It may be remembered that a similar difficulty in infecting animals with the cholera vibrio by means of the alimentary tract exists, although this can be effected if the acid contents of the stomach be first neutralised with alkali, as was done by Koch. A similar method had been used with the typhoid bacillus successfully. A true infection follows the injection of the virulent bacillus into the peritoneal cavity or into the venous system, and also under the skin, although to a lesser extent; that is, there is a dissemination of the bacillus through the organs of the body and the blood. In some animals, however, it may be absent in the blood, and this was found also by Remlinger in his cases of intestinal infection.

An interesting point in the infection of the animal body by the typhoid bacillus is that, although the non-virulent forms of the bacillus are not toxic they may become so, and may infect the body when products of certain other micro-organisms are injected at the same time. I have previously mentioned these experiments, and the chief point which is noteworthy is that the injection of the products of the bacillus coli into the peritoneal cavity at the same time as the injection of the living typhoid bacillus under the skin aids the distribution of the bacillus throughout the body. At death in such cases it is found in the peritoneal cavity and in the organs of the body. This does not occur if the non-virulent typhoid bacillus is injected by itself. The products of other micro-organisms will also do this.

In some cases enteric fever appears to be a pure infection of the typhoid bacillus; in other cases it is a mixed infection, or there may be infection after the acute disease is over, usually by pus organisms. It has been found in some cases in the course of typhoid fever that the bacillus coli, which is naturally found there, becomes more virulent than it is in life and increases greatly in number. It is possible, therefore, that these two organisms react on each other, one aiding infection by the other. It is known that the products of the bacillus coli aid infection by the typhoid bacillus, and cases in which there is infection by the bacillus coli during the course of typhoid fever have been observed—for example, in abdominal abscesses and cystitis.

It has been much discussed whether enteric fever is a primary intestinal infection, or whether it is a general infection with an intestinal lesion; that is, whether the bacillus primarily infects the Peyer's patches, and from there is distributed to the mesenteric glands and the spleen, or whether the micro-organism is introduced into the body in some other way (unknown), and infects the body, producing an enlargement of the spleen and ulceration of the Peyer's patches in the intestine as part of the general infection.

The arguments which have been used for considering enteric fever a general infection with a secondary intestinal lesion are not very satisfactory. It has been said that, inasmuch as the bacillus is not constantly found in the motions and is found in the urine, it would appear that there are not many bacilli in the intestine, such as would exist if the intestine were primarily infected. There is

nothing whatever in this argument, inasmuch as even if there were a primary intestinal infection, we can readily see that the bacillus might not be discharged in the faeces in sufficient numbers to be readily found. Moreover, if there is a great increase in the number of bacillus coli in the intestinal tract, not only is there great difficulty in finding the typhoid bacillus in the presence of large numbers of this micro-organism, but the more vigorous bacillus coli might actually beat out of the field the less vigorous typhoid bacillus.

As regards the passage of the typhoid bacillus in the urine, this would as readily occur from an intestinal infection which is followed by a general infection as when there was a general infection primarily.

Another argument which has been used, and which is perhaps somewhat stronger than the first, is the result of Sanarelli's experiments. He found that, however introduced into the body—whether through the venous system or subcutaneously, or into the peritoneal cavity—the stress of the disease produced by the typhoid bacillus and its poison was on the abdominal organs and chiefly the intestines, which showed what he described as "acute mucous inflammation." The Peyer's patches were described also as swollen. From these results Sanarelli was inclined to look upon the infection as a general one with a local intestinal lesion. But the results obtained by him are not due to an infection of the body by the bacillus, but to the action of the poison of the bacillus. The effect on the intestine is due to the poison and not to the infection. It is not due to the fact that the bacilli introduced under the skin or into the vein, so to speak, get buried in the mucous membrane, where they produce a lesion, but it is due to the selective action of the poison on the small intestine, a selective action which, as we have seen, is not limited to the typhoid poison, but is also possessed by the poison of Gärtner's bacillus and of the bacillus coli, and also of the two vegetable poisons (abrus and ricin).

The result of producing an intestinal lesion by the subcutaneous or intravenous injection of a poison is not limited, therefore, to the typhoid bacillus, and the question is really one, not of the action of the bacillus itself, but of the action of the poison introduced with it. It has been a question in these intestinal lesions whether ulceration can be produced by the intravenous injection of a poison. Ehrlich stated that ulceration sometimes followed poisoning with ricin and abrus. In my own experiments such ulceration was never observed, and they were not observed by Flexner. From what we know of other intestinal affections, the view that the infection in enteric fever is primarily intestinal is the more logical. The part of the intestine affected—namely, the Peyer's patches—is the least protected part of the mucous membrane, and is a tissue of only slight metabolic activity, covered with a single layer of epithelium, with no villi; whereas the rest of the mucous membrane is covered with villi, which are more or less constantly in a state of active metabolism. Moreover, in tuberculosis produced by feeding, the Peyer's patches of the intestine are the first infected, and I cannot myself conceive of any general intestinal ulceration occurring in the absence of a local infection. In tuberculosis, ulceration of the intestine never occurs as the result of general infection, and the ulcerations of the upper part of the small intestine which sometimes occur in septicæmia and pyæmia are always few in number (one or two), and are irregularly placed.

I wish, in conclusion, to express to you, sir, and to the College my sense of the great honour you have conferred upon me by appointing me to deliver these Croonian Lectures; and I gladly acknowledge the great help I have received from my two assistants in the investigation—namely, Dr. Greig, my assistant in bacteriology at University College, and Dr. R. Row, of Bombay. Both these gentlemen, by their devotion and skill, have contributed greatly to whatever success has attended the investigation.

NOTE AND REFERENCES.

- ¹ Simon Flexner, *The Pathology of Tox-Albumin Intoxication*, *Johns Hopkins Hospital Reports*, Baltimore 1897.
- ² See C. J. Martin, *Physiological Action of Venom of the Australian Black Snake*, R. S. New South Wales, 1895. Martin gives the value of the anthrax albumins as 80, quoting from my first experiments. My later experiments are as in the table, namely, 3,000. See also Calmette, *Ann. de l'Inst. Pasteur*, vol. viii, 1894.
- ³ *Ann. de l'Inst. Pasteur*, vol. xi, p. 829.