ART. VIII.—*Antitoxin in Diphtheria*.^a By H. C. MACQUAIDE, M.D., Univ. Dubl.

ANTITOXIN, or antidiphtheritic serum, began to be used as a remedy for diphtheria about twelve years ago. Its use and preparation were suggested by Behring and Kitasato in 1890, who were experimenting with a serum for the neutralisation of the tetanus virus, and suggested the application of the same principles in the case of diphtheria. It was first tried in von Bergmann's clinic in Berlin. The serum was very weak, and the dosage, as we know now, entirely insufficient. The serum was at that time prepared by using small animals.

Ehrlich and Wassermann, by using goats instead of the smaller animals, obtained a serum 20 to 60 times stronger than before. This they used the following year in over 200 cases, with a mortality of 23 per cent.; this was good compared with the previous mortality of 35 per cent.

Kotz the same year prepared a serum from horses, which he used in 163 cases with even better results.

From this time the attention of the general medical world was drawn to the subject, and antitoxin was widely used. The results at first obtained were apparently so contradictory that it was held by many to be useless, if not dangerous. In some cases the patients injected developed tetanus, and this naturally retarded its general use. The cause of this accident was soon discovered and removed, and the serum which is now prepared can be relied on to be free from the tetanus bacillus. Still it cannot be said that we have yet obtained an ideal serum, for there is little doubt that the use of the present serums is often followed by complications such as rashes, joint-pains, and pyrexia. Now these complications are believed to depend on something in the serum, which has no connection with the antitoxin but is connected with the particular horse from which the serum was obtained, and also with the concentration of the serum. These are defects which in time, therefore, can be removed.

^a A Thesis for the Degree of Doctor of Medicine of the University of Dublin, read December, 1903.

Antitoxin serum has been usually employed subcutaneously, and also both by mouth and rectum, and as an intravenous injection. Its use both by mouth and rectum has not been successful. This was only to have been expected from a consideration of Ehrlich's theory of immunity, which is now generally accepted, and which assumes that the immunising or antitoxin value of a serum depends on the molecular arrangement of the antitoxin body, which is a proteid substance, and would be entirely altered in the process of assimilation from the digestive tract.

His theory, too, throws considerable light on the reasons why the antitoxin has not been more successful as used heretofore, for, remembering the extraordinary complexity of the proteid molecule, it explains the urgency there is for using the antitoxin as soon as possible.

My experience of antitoxin extends over the last four years, during which time I have used it in about 100 cases of diphtheria. I have always used it subcutaneously. This method is open to the objection that abscess may follow at the seat of injection.

Having prepared the skin so as to make it as aseptic as possible, I usually injected the serum under the loose skin beneath the angle of the scapula. I have never found an abscess follow the injection. The method is not usually painful, even for large quantities of serum. This seems partly to depend on the sex of the patient, for I have almost always found in children that the males were more sensitive to the pain of injection than females.

The first case of diphtheria in which I used antitoxin was the most virulent I have seen, the patient dying within three days from the onset of her illness. I saw her on the third day of the disease, and found her almost comatose, and with every appearance of profound toxæmia. She was roused with difficulty; her extremities were cold, her respirations shallow, and pulse feeble and rapid. On examining her throat I found both hard and soft palate, tonsils, and pharynx covered with membrane. I injected 4,000 units of antitoxin subcutaneously in the abdominal region without any apparent effect, as she died a few hours later.

This case might lead one to doubt the efficacy of antitoxin in cases so severe, but more recent experience has shown that even in such cases antitoxin, if properly administered, may save the patient. I refer to the method of intravenous injection. This was first practised last year by Dr. Cairns, of Glasgow. His results show that the intravenous method may be successful even in the most severe cases. His description of the case in which he first practised this method is as follows:—"The patient was pulseless, and apparently moribund, the extremities as well as the surface of the body being cold and livid, the lips were swollen and cyanotic, the face puffy and yellowish-white in colour; the heart was beating very rapidly, the respirations 60 to the minute, there was laryngeal obstruction; tracheotomy was performed with little relief, and then 26,000 units of antitoxin were injected into the median basilic vein. The patient slept well after the operation. For 36 hours she scarcely improved, during which time she had repeated injections of strychnine and caffeine, which had a beneficial effect on the pulse; then signs of improvement began to show themselves coincidently with a copious discharge of muco-purulent matter from the tube. From this point the patient steadily improved, and made a good recovery." This is not a solitary case, as Dr. Cairns has now a series of 50 consecutive cases, in 20 of which he has used the method of intravenous injection. He was led to try the intravenous method from his experience with plague serum, where he found that the serum seemed to lose a large percentage of its efficacy in passing through the lymphatic circulation; this, too, is in accordance with Ehrlich's theory, for assuming the antitoxin to be protoplasmic and not a fixed chemical substance, it can easily be imagined that it might be fundamentally altered in passing through the lymphatic glands. The result of his 50 cases gave a mortality of only 6 per cent.

The value of antitoxin depends greatly on the time of its administration, independently of the amount or method of using it. I found in my cases that if injected the first day in sufficient quantity (and latterly I never injected less than 2,000 units) it usually cut short the attack, and in some cases so rapidly that I was compelled to doubt the

accuracy of my diagnosis. The following case of diphtheria in which I injected antitoxin the first day is typical of many in my experience :—The patient, a girl aged five years, had been heavy and drowsy all day. I saw her that evening and found her in a feverish condition. On examining the throat I found the tonsils and part of the pharynx and soft palate covered with a tenacious membrane. I attempted to remove some of it from the soft palate, which bled easily. I then injected 2,000 units of antitoxin, and the following morning she was much better; the drowsy, stupid condition had passed off, and the membrane had begun to separate at the edges, rolling off as it were, to be finally coughed out. This was the usual course of the pharyngeal cases, if injected the first day. This corresponds with the general experience for Dr. Otto Jelisch, who has analysed over 127,000 cases from all sources, and finds that cases injected with antitoxin the first day give a mortality of only 5 per cent.

As a rule, the cases injected with antitoxin the first day may be expected to make a rapid recovery. The exceptions in my experience were those cases in which the larynx was involved, while a reference to a report of the Metropolitan Asylums Board shows, as might be expected, that in cases of mixed infection where streptococci, and more often staphylococci, are found in the membrane, antitoxin is not nearly so successful.

The following is a laryngeal case :—The patient was a boy aged about five years, he was in the dull, toxæmic condition which is characteristic of severe diphtheria. There was no membrane visible; he had a croupy cough, and inspiratory stridor. I injected 2,000 units of antitoxin, and had him placed in the steam tent. The following morning, as he did not appear much better, I injected another 2,000 units. He was very restless, cyanosed, and apparently sinking. I advised a tracheotomy; this was refused. Before the evening, however, he began to cough more softly, and from that time he made an uninterrupted recovery.

My next laryngeal case was in a child who had previously had several attacks of simple catarrhal laryngitis. I did not inject until the third day. In this case, too, I injected the serum into the abdominal region, but unsuccessfully, the

patient dying the following day. This case shows both the necessity of early injection and of larger doses of the serum.

It has been stated that the use of antitoxin predisposes to the occurrence of post-diphtheritic paralysis. I have had but one severe case of this kind. It was fatal. The patient, a boy aged ten years, had his pharynx and tonsils severely affected; the membrane, however, did not spread to the larynx. I injected him with 2,000 units of antitoxin the first day of his illness. The following day the membrane separated and his general condition was much improved. On the 9th day, however, he began to have difficulty in swallowing from paralysis of his soft palate, and later his heart began to fail. He died of syncope on the 18th day of the disease.

In referring to the various statistics relative to this point, it would appear that paralysis is more frequent with the use of serum, and this can be explained by the fact that in serum cases, terminating fatally, life is much prolonged, and thus the paralysis has time to develop. Ransom's experiments on animals throw much light on this question, for he finds that paralysis depends on the toxicity of the inoculation, and that neutralised doses of toxin and antitoxin do not appear to cause paralysis. It is thus fair to assume that in severe cases, with a great deal of toxæmia, paralysis is likely to occur if the patient lives long enough, and that if antitoxin is given early and in sufficient amount paralysis will probably be prevented.

By thus prolonging life in these cases opportunity is given for the use of other means of eliminating the toxin.

Schoull, of Paris, in an apparently hopeless case of post-diphtheritic paralysis, which had been treated with antitoxin, injected a litre of Hayem's serum into the median basilic vein to wash the blood as it were. This gave a marvellous result; the patient in a dying condition in the morning, appeared out of danger in the evening, and he made a complete recovery.

As a preventive of diphtheria antitoxin has proved remarkably successful. In some large institutions, in which formerly the disease was never absent, since the introduction of the practice of giving immunising doses of antitoxin, the

disease has been completely exterminated. It has been found that antitoxin only confers immunity for about three weeks.

My experience with antitoxin, then, would suggest the following conclusions:—Every case of diphtheria should be treated with antitoxin; the serum must be given early and in large doses; and all individuals exposed to infection should be given immunising doses of antitoxin; finally, the serum is a specific in diphtheria if properly used.

ART. IX.—*Some Public Health Problems in Ireland.** By SIR JOHN W. MOORE, M.D., D.P.H., Univ. Dubl.; F.R.C.P.I.; President of the Section of State Medicine in the Royal Academy of Medicine in Ireland.

INTRODUCTORY.

FOR the third time I have been called to preside over this Section of the Royal Academy of Medicine in Ireland. It is hardly necessary to say that I look upon such a mark of confidence as a very signal and gratifying compliment, of which I may well be proud, and for which I return you my most hearty thanks.

On February 5, 1885, I addressed this Section—or, as it was then, Sub-section—of the Academy on “Sanitary Organisation in Ireland in its Medical Aspect.” Two years later, on February 3, 1887, the subject of my Inaugural Address was “The Present and the Future of State Medicine.”

In the seventeen years, which have passed away since the latter date, State Medicine has made unexampled progress in all its departments—Sanitary Organisation in Ireland, on the contrary, has advanced “with halting steps and slow.” Yet substantial advance has taken place in many directions even in this country.

NOTIFICATION.

In 1887 I had to deplore an uncompromising opposition to the principle of Compulsory Notification of Infectious Diseases on the part of the vast majority of the Medical

* An Address inaugurating the Session of 1903–1904, delivered before the Section of State Medicine in the Royal Academy of Medicine in Ireland, on Friday, February 12, 1904.