Active immunisation against diphtheria : the present position / by R.A. O'Brien.

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ACTIVE IMMUNISATION AGAINST DIPHTHERIA.

THE PRESENT POSITION.

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FOR the modern history of active immunisation in man we need not go further back than to Theobald Smith's suggestion (1909) that mixtures of toxin and antitoxin should be used for the immunisation of human beings. The first attempt to immunise considerable numbers of human beings was made by von Behring who examined various combinations of diphtheria bacilli, toxin, and antitoxin; the method settled down (1913) into the one that has been in general use until recently in Austria and Germany. Broadly speaking, this consisted in the use of an under-neutralised mixture of toxin and antitoxin—i.e., one in which there is slightly more toxin present than can be neutralised by the quantity of antitoxin. The mixture is therefore toxic to animals.

v. Behring's Mixtures.

With regard to von Behring's mixtures, Dr. van Boeckel (1924) in his report to the League of Nations writes :—

> "We do not know the exact composition of von Behring's T.A. mixtures. The fact that they are administered intradermally is not calculated to simplify the technique, which is rendered still more complicated by the fact that the proper sensitising dose has to be discovered before the vaccinating dose can be administered."

This method seemed to be rather difficult to carry out in practice and is falling into disuse in its original home where American mixtures and practice have recently begun to attract attention.

A new and brilliant chapter was opened by Park and co-workers in New York in 1913. They first used a mixture of toxin and antitoxin containing in 1 c.cm. 3 L+ doses of toxin, under-neutralised to such an extent that doses of from 1 c.cm. to 5 c.cm. produced paralysis or death in guinea-pigs. Within the past few years, Park has replaced his original mixture by a second toxin antitoxin containing in 1 c.cm. only 0·1 L+ dose of toxin, though in each cubic centimetre of this mixture the same amount of toxin is left unneutralised as in the original 3 L+ mixture. This second mixture was tested on man in parallel with the original one and gave fewer local reactions, whereas its immunising power was probably

better. It is now in routine use in New York and most of the United States of America.

The two American accidents in active immunisation occurred apparently with preparations similar to Park's original mixture. It is now possible to make some statement about the first of these accidents, that at Dallas, the cause of which is clearly understood. A certain volume of toxin added to a certain volume of antitoxin may give a neutral mixture—i.e., one that is harmless to guinea-pigs when injected. But if the toxin be divided into two portions, the first of which is added and thoroughly mixed with the antitoxin, while the second portion is added subsequently, a toxic mixture may result. This is the well-known Danysz phenomenon. The original tests of the mixture used at Dallas had been carried out thoroughly and were apparently completely satisfactory. Owing to an unfortunate mistake the applicability of the Danysz phenomenon to the mixture in question, when, after the first tests the proportions of toxin and antitoxin had to be adjusted, was overlooked, and a toxic mixture resulted. The second of these accidents (Concord, 1924) was caused by the accidental exposure of a mixture to intense cold for several days, when sufficient toxin was released to cause severe reactions in several dozen children. There were, fortunately, no deaths. The explanation of this phenomenon has been given by Glenny and co-workers (1925) in this country. Now that this risk is recognised it is very unlikely that this same mishap will again occur. A very large number—probably several hundred thousand—injections of these American mixtures have been given with complete safety except in the two well-understood instances mentioned, and with excellent immunising efficiency.

With regard to the Vienna (Baden) accident (THE LANCET, Oct. 3rd, 1925, p. 713), it has apparently been impossible to obtain for examination in England a specimen of the mixtures used, so that no close comparison of the Vienna lethal preparation with the American or English mixtures has been possible. It is not easy to deduce from the published account by Helmreich (1925) exactly how the mixture was constituted, although it is clearly stated that it was made of toxin and antitoxin. Presumably the aim was to produce a mixture similar to those used by Park. If, as is suggested, a non-toxic mixture of toxin and antitoxin dissociated under ordinary conditions of storage and became toxic, this phenomenon has not been met with in the very extensive experience of American and English workers.

Detoxicated Toxin.

The next development in the history of immunisation was the use (without antitoxin) of toxin which had been so treated as to deprive it of most or all of its original toxicity while leaving its immunising power still high. In this "toxoid" class come the

aged toxin, &c., used by Park (1923), the formalinised "toxoid" made by Glenny and Hopkins (1923), and used by O'Brien and co-workers in England, and the formalinised "toxoid" or "anatoxin" used by Ramon and colleagues (1924) in Paris.

Theoretically, preparations of this toxoid class should be preferable to Park's first or second mixtures, for they can be made completely atoxic to the guinea-pig and they are free from the additional complication of having antitoxic serum present. These toxoids are being tried cautiously in the three countries mentioned; it is possible that they will eventually entirely replace the other prophylactic preparations, but it is too early yet to predict this with any certainty. The immunising power of toxoid is high, but it is apparently rather liable to cause reactions when injected. The concentrated toxoid preparations of Watson and Glenny (1924) may be added to this class; though they produce a high immunity in animals and are atoxic, they have not yet been used in human practice to any large extent.

Another class of prophylactic is represented by the toxoid antitoxin mixtures made and used widely in England. Glenny and co-workers (1924) discovered that if one makes a toxin non-toxic by treatment with formalin—a preparation which has high immunising power—and adds a certain volume of antitoxin to the toxoid, the immunising power of the toxoid is not materially reduced. A typical mixture of the kind would contain in 1 c.cm. about 0·1 c.cm. of "toxoid" made by formalinising toxin with an original minimum lethal dose of between 0·002 c.cm. to 0·001 c.cm. until the lethal dose was reduced to about one-hundredth of its former value or, better, to the stage where 5 c.cm. produced no symptoms in guinea-pigs. In addition to the toxoid, the mixture contains a quantity of antitoxin varying from 25 to 50 per cent. of the amount corresponding to the original neutralising value of the toxin. The mixture which gives the best immunity index is the one chosen for use. This combination is non-toxic to guinea-pigs but gives excellent immunising results in these animals and is apparently a "safe" mixture. Many thousands of doses have been given during the past two years. Even four or five years ago, when the first toxin antitoxin mixtures of the American type were used in England, the standard of toxicity adopted was below that permitted by the official Washington regulations. These latter allow the use of mixtures of which 1 c.cm. will produce paralysis in all the animals injected and death in a small number.

It was found by the aid of the Glenny-Allen (1923) "immunity index" that it was possible to prepare toxin antitoxin mixtures of such low toxicity that 1 c.cm. did not produce paralysis or death, while a dose of 5 c.cm. would cause paralysis or death in either none or at most a small percentage of the guinea-pigs injected, and yet would rapidly produce

immunity. Most of the published work in England was apparently done either with mixtures of this type or of the toxoid antitoxin type previously mentioned. These latter preparations appear to have a double margin of safety. They contain toxoid mixed with a quantity of antitoxin and thereafter diluted ten times. The toxoid is itself almost or completely devoid of toxicity. This change from toxin to toxoid is apparently an irreversible one, for in all the intense study of this field by various workers during the past few years there has arisen no evidence suggesting that toxoid in this condition can revert to toxin. Even if this very unlikely change took place and some of the toxoid were reconverted to toxin, the mixture contains sufficient antitoxin to neutralise a large amount of toxin.

Lines of Future Progress.

With regard to possible progress in the future, the main effort is being directed along three lines. The first is to provide active immunisation for children of pre-school age who are likely to be exposed to diphtheria. Most of the work hitherto has been carried out with children aged 6 and upwards, but a great deal of diphtheria occurs in younger children. The second is to increase the immunising efficiency of the prophylactic so that one could obtain the same efficiency of immunisation with two injections or even one, which one now obtains with three. Along these lines progress must be slow. It is easy to make immunising mixtures of very high efficiency in the laboratory. Thus Glenny and co-workers have described a preparation which will make animals negative to the Schick test in 12 days, but the transfer of such work to human practice must be slow, for the greatest caution is necessary. The other effort is to shorten the number of tests and injections by combining them. Park is directing effort to a mixture which when injected will indicate the response to the Schick test and at the same time will act as an immunising agent.

In England there are at present (1926) being tried mixtures which will, when injected intracutaneously into animals, produce a Schick test reaction, and at the same time supply an efficient immunising stimulus. One can thus, when each immunising intradermic injection is given, get an indication of the condition of the patient and know exactly when to cease the injections.

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