Active immunisation against diphtheria : to the editor of the Lancet / [R.A. O'Brien].

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ACTIVE IMMUNISATION AGAINST DIPHTHERIA.

To the Editor of THE LANCET.

SIR,—You have done much during the past few years to help those interested in the public health aspects of the Schick test and active immunisation against diphtheria. They will owe you a further debt for the information given by your Vienna correspondent in your issue of Nov. 22nd, 1924, relating to the recent accident in that city, for it is only by obtaining full information such as your correspondent tried to get, that those who are using these methods can feel full confidence in their work.

The Vienna accident is the second reported within the past few years. In connexion with the first, in January of last year, Kelley (1924) reported that toxic symptoms occurred after the injection of toxin antitoxin mixture into a number of children at Concord and Bridgewater, Mass. A careful inquiry was made and it was found that some bottles of a batch of prophylactic mixture had been exposed to a very low temperature. After thawing, the contents of these bottles proved to be very toxic, whereas the toxin-antitoxin mixtures which had not been frozen were non-toxic. The effect of intense cold upon toxin antitoxin mixtures was investigated experimentally by a number of American workers; some found that freezing increased toxicity, others did not. Mr. Glenny and Mr. Pope have investigated the problem at these laboratories and are preparing a paper for publication from which they have kindly allowed me to quote. They found that the toxicity of the mixtures they worked with did not increase after freezing. It occurred to them that the local concentration of the phenol or other antiseptic present, which takes place during freezing and thawing, would vary with the composition of the mixture and the exact physical conditions during the freezing and thawing, and that certain concentrations of phenol might be more destructive to the antitoxin present than to the toxin. They therefore tried the effect of various concentrations of phenol first upon antitoxin and toxin separately and finally on mixtures of toxin and antitoxin. They found that, if they made the phenol concentration 5 per cent. in a solution of antitoxin containing three

units per c.cm., the antitoxin quickly disappeared. A similar concentration of phenol was added to a solution of toxin containing 3 L+ doses per c.cm.; about 10 per cent. of the original toxicity remained. And finally they found that non-toxic mixtures became toxic, without freezing, if 5 per cent. of phenol were added. Trikresol acted in the same manner. We have thus available a simple explanation of the increase in toxicity observed at Concord. During the freezing and thawing a local concentration of phenol occurs and the interesting dissociation and destruction of antitoxin takes place.

The only report of the second accident in Vienna available at the time of writing is that given in your issue of Nov. 22nd. Your Vienna correspondent writes: "It is well known that the antitoxin is liable to disintegrate much more quickly than the toxin." You, Sir, evidently held the same view when you wrote: "It is not safe to risk toxin and antitoxin becoming dissociated in the mixture by long keeping." I feel that this explanation is difficult to reconcile with the general experience of workers in America and England. The Bacteriological Committee of the Medical Research Council, in referring to toxin-antitoxin mixtures, say: "No increase in toxicity has ever been observed on keeping." This view is apparently in accordance with American experience, for the official recommendation of the Bureau of Hygiene is that slightly toxic mixtures should be held until the toxicity is so reduced that the mixture complies with the official standard.

Our own experience agrees with this. Mr. Glenny has in preparation a paper giving the details of tests of the toxicitity of mixtures from three months to four and a half years old. Samples were kept at room temperature, in the cold room, and in the incubator, but in no instance has there been an increase of toxicity. I may remark here that the mixtures we have worked with in these laboratories have always been adjusted to have a toxicity lower than that prescribed in the official U.S.A. regulations. Whereas 5 c.cm. of the mixtures officially allowed in America may kill acutely two out of five guinea-pigs, and may kill the remaining three with paralysis in 15 to 35 days, we have from the outset made a practice of using mixtures of which 5 c.cm. would not kill any of the animals injected within 15 days; few of the guinea-pigs receiving 5 c.cm. of the various batches of toxin-antitoxin mixture died within 21 days, and many lived and developed no paralysis. The more we know of these accidents the more certain we can be that similar accidents will not occur in future.

It is obvious that no safeguards can overcome the danger if the toxicity of all mixtures is not adequately tested before their issue. Now that the danger from freezing is known, we are justified in concluding that an accident similar to that at Concord will not again occur. With regard to the second, we must await further information, but there is no evidence that the explanation put forward as the cause of the Vienna misfortune is applicable to the mixtures in use in England.

It is possible that the process of active immunisation may be considerably improved by the use of formalinised toxin, which is practically non-toxic. This interesting method of modifying toxin was apparently first described by Salkowski (1898) and investigated and used by Loewenstein in 1904 (1914). It was in use in these laboratories in 1904 for the immunisation of horses. Glenny and Sudmersen (1921) found that guinea-pigs could readily be immunised with this toxoid, and in 1923 Glenny, Allen, and Hopkins suggested its use for human immunisation. It was, later, independently discovered and investigated by Ramon (1924). A considerable amount of work with formalinised toxin has been carried out by Park and Zingher in New York, by Ramon in France, and at these laboratories. The results so far obtained are encouraging, but one is not yet ready to advocate the immediate complete replacement of toxin-antitoxin mixtures by toxoid. We can advance safely only if we proceed slowly.

May I comment on the expression "Schick serum must be fresh"? It would seem that the use of the expression "serum" when applied to mixtures of toxin with antitoxic serum is not in accordance with ordinary pathological practice, and although we owe the valuable test to Prof. Schick, whose name it bears, he had but little to do with the introduction of toxin-antitoxin mixtures, and his name is not usually attached thereto.

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I am, Sir, yours faithfully,

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