elevation and because there is no advantage in completely immobilizing the shoulder-joint, which of course is never quite immobilized on an abduction splint.

Comment

The application of either splint is really not difficult and merely requires a little practice, which can be put in with great advantage on orderlies or assistants until the surgeon, or whichever member of his team is to do the actual job, is able to carry it out quickly, easily, and confidently. But it is quite essential to have the patient's conscious co-operation, and for this reason neither abduction splint nor plaster should ever be applied to a patient just recovering from an anaesthetic. If a general anaesthetic has been given the arm should merely be bandaged to the trunk as in the first-aid treatment of a fracture, and the splint or spica applied as soon as the patient has fully recovered from the anaesthetic. Skilled and gentle application, especially with an intelligent and skilled assistant to hold the limb *under slight traction*, is practically painless.

DIPHTHERIA PROPHYLAXIS

OPTIMUM DOSAGE AND TECHNIQUE IN USE OF ALUM-PRECIPIATED TOXOID

BY

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Of the reagents available for the specific prevention of diphtheria there can be little doubt that, volume for volume, the most highly antigenic is alum-precipitated toxoid (A.P.T.), the preparation of which was first described by Glenny and Barr (1931a). Thus, its value is widely appreciated and utilized in the immunization of horses; laboratory experiments on guinea-pigs have shown A.P.T. to be a better antigen than unmodified toxoid (Park, 1937; Jones, 1938), and Glenny and his colleagues (1931b) have provided the explanation of why this should be so. In human work, when used by one injection, its results, while admittedly erratic, are unapproached by those of any other compound employed as a single dose; while when used in two doses, as it always should be, it consistently produces a Schick-negative rate of over 98 per cent. (Chesney, 1938, 1939; Parish, 1936; Thomas, 1937; Lewis, 1939b, 1939c). Even, however, when two injections are employed the procedure may be open to improvement, as it is the purpose of this paper to demonstrate.

Many workers have carried out antitoxin estimations on the blood of persons injected with two doses of A.P.T. (Jones and Moss, 1937; Fraser and Halpern, 1937; Schall, 1938; Paschla, 1939; Volk and Bunney, 1939). For the most part these have been on small numbers of cases tested about three months after the second dose. Until, therefore, antitoxic estimations on a large scale are performed knowledge of the exact degree of antigenicity of A.P.T. in man must remain vague and conjectural. An attempt at such an investigation is now being made in Croydon, under the supervision of Dr. O. M. Holden.

Blood Antitoxin Values Sixteen Months after Two Injections of A.P.T.

It is not possible at this stage to give the full results of this inquiry, which is still proceeding. When A.P.T. was first used in Croydon, some two years ago, it was given

in a dosage of 0.1 c.cm. followed in a fortnight's time by 0.5 c.cm. in the same arm. Although it was realized that, immunologically, a month's interval was better, it was considered that a fortnight's interval, under the circumstances then prevailing, presented fewer administrative difficulties. Of the 100 cases so treated it has been possible after a mean period of sixteen and a half months to obtain blood samples from forty-nine. All cases were originally Schick-positive, and the mean age of the children at the time of inoculation was $9\frac{1}{2}$ years. All the cases were from two schools that had experienced a mild outbreak of diphtheria for some weeks before and during the time when the inoculations were being given. The antitoxin levels obtained were as follows.

Distribution of Blood Antitoxin in Forty-nine Children Sixteen Months after the Second of Two Fortnightly Injections of A.P.T. (0.1 and 0.5 c.cm.)

No. of children	Antitoxin Titre in Units per c.cm. of Blood										
	5	2	0.5	0.35	0.2	0.1	0.04	0.02	0.01	0.004	0.002
	1	1	1	1	2	5	9	7	11	7	2

Parish and Wright (1938) have pointed out that antitoxic immunity must be regarded quantitatively as there is no fixed level of immunity. An arbitrary level may be taken to be from 0.005 to 0.05 antitoxic unit per c.cm., a scatter of 0.045 A.U. around 0.01 A.U. In this way the above forty-nine children may be grouped into three classes: (1) Eleven, or 22.45 ± 6.1 per cent., had more than 0.05 A.U. per c.cm., which should be enough to neutralize the toxin produced by any but the most massive infection: these are immune. (2) Twenty-seven, or 55.1 ± 7.6 per cent., had between 0.005 and 0.05 A.U.: while these have less antitoxin than the previous group they may still be considered potentially immune. (3) Eleven, or 22.45 ± 6.1 per cent., had less than 0.005 A.U. per c.cm. It is conceivable that sudden invasion with large numbers of virulent organisms (as from an actual case) may cause clinical symptoms in cases of this group before they can react to the secondary stimulus: these are potentially susceptible. Allowing for chance variations, this proportion— 22.45 ± 6.1 per cent.—is unlikely to differ by more than twice its standard error in samples of the same size; that is, it may be 34.65 per cent. or 10.25 per cent. If this lower figure is taken it may be felt that 10 per cent. is an undesirably high proportion to have as little as or less than 0.005 A.U. only sixteen months after the injections, for this level may not give high protection against sudden invasion by virulent organisms. It is therefore necessary to consider means of increasing the antigenic effect.

Greater efficiency may be obtained in two ways without raising the total number of injections. First, the only reason for limiting the initial dose to 0.1 c.cm. is the fear of reactions. The results in the Croydon cases demonstrate quite clearly that little or no trouble will be experienced in children below 8 years, and, therefore, below this age the initial injection should be 0.5 c.cm., as Bousfield (1938) has suggested. Over 8 years it is wise to limit the dose to 0.25 c.cm. Chesney (1939) quotes work by Jensen (1937) as suggesting that there is "no immunological advantage in giving 0.5 c.cm. as an initial dose." While this may be so, it is quite common to find, even with careful work, a certain quantity of antigen escaping from the puncture when the needle is withdrawn, and in many cases it is likely that the effective dose is less than that actually injected. By giving 0.25 or 0.5 c.cm. allowance is made for this. The interval between the injections should never be less than one month.

Another observation of some interest, and perhaps of value, is the following. Accurate records were not kept, their possible significance not being realized, but it was noticed that the second injection of A.P.T. at the same site as the first may not cause any increase in the amount of induration which, as is well known, forms at the site of the first injection. The first injection causes local hyperaemia, with congestion of the tissues and increased lymph flow—the normal response to the presence of a chemical irritant. When the second dose is given in the same place as the first, compensatory hyperaemia is already present, and so the A.P.T. is removed more quickly, the slow absorption and consequent prolonged antigenic action, which Glenny, Buttle, and Stevens (1931b) showed to be so important, being counteracted. To obviate this the second injection should be made in the opposite arm; in this way, by ensuring protracted absorption, the maximum effect is likely to be produced.

Conclusion

Allusion has been made elsewhere (Lewis, 1939a, 1939b) to the many methods by which anti-diphtheria schemes in this country are conducted. According to a survey of the schemes of some 150 of the larger urban authorities, made by means of a questionnaire issued by Dr. O. M. Holden, A.P.T. by two injections is used in about 40 per cent. of those studied, in many cases in a dosage of 0.1 c.cm. and 0.4–0.5 c.cm. at fortnightly or three-weekly intervals. A.P.T. by at least two injections, properly spaced and given in adequate dosage, possesses so many advantages over other antigens that it would be a misfortune of the greatest magnitude if it should fall into disrepute through wrong technique. It will be shown in a later paper that in two doses of adequate size, and properly spaced, it will give results that compare very favourably with those given by three doses of unmodified toxoid. Few would cavil at the desirability for some measure of uniform practice in diphtheria immunization, which undoubtedly is greatly hampered by the lack of such a standard. A.P.T. in two injections, with the modifications here advocated, supplies this need, and could with advantage be utilized by all authorities responsible for the control of diphtheria. It is of the utmost importance, however, that proper methods be used. Those advocated are: (1) the dosage to be 0.5 c.cm. and 0.5 c.cm. in children under 8 years; in children of 8 years or more the first dose to be 0.25 c.cm., to be followed by 0.5 c.cm. if there is no reaction; (2) the interval between the doses to be in no case less than four weeks; (3) the injections to be given in opposite arms.

Summary

The results are given of antitoxin titrations in forty-nine children who were bled sixteen months after 0.1 c.cm. of A.P.T. followed in two weeks by 0.5 c.cm.

It is shown that sixteen months after A.P.T. administered in this fashion at least 10 per cent. of children may be susceptible to a large dose of virulent organisms.

Certain modifications in dosage and technique are advocated as a means of increasing the antigenic effect without increasing the number of injections. It is suggested that this procedure may with advantage be adopted by all scheme-making authorities.

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BENZEDRINE SULPHATE

ITS USE TO INTERRUPT AVERTIN ANAESTHESIA

BY

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Avertin, used as a basal anaesthetic, has the great disadvantage that once it has been absorbed into the system it cannot be withdrawn. The counteraction of avertin, and especially of an overdose, has attracted the attention of many observers. Bolliger (1932) experimented with sodium thiosulphate, and he found that although this drug prevented the onset of narcosis it was of no avail in counteracting an overdose. Pribram (1929) experimented with thyroxine to expedite the detoxication, but considered that the drug acted too slowly to be of service in an emergency. Caffeine sodium benzoate has also been tried (Herzberg, 1928; Speidel, 1930). This was found to interrupt avertin anaesthesia in animals, but its action as a respiratory stimulant in man is doubtful, although Herzberg claims that it interrupts avertin narcosis, with slowing and deepening of respiration. Ephedrine has been used (Widenhorn, 1932) with a view to the restoration of the fall in blood pressure. The rise produced is not evident in all cases. Adrenaline frequently produces cardiac irregularity, and in heart-lung preparations ventricular fibrillation is sometimes seen. Kennedy (1932) observed that the first inhalation of ether often produced a marked improvement in the patient's condition. Those patients not benefited by ether were rapidly relieved by the administration of 5 per cent. carbon dioxide in oxygen. Killian (1931), Mörl (1931), and Kennedy (1932) tried coramine and found it an even better antidote. In man 2 to 3 c.cm. of coramine injected intramuscularly, and repeated if necessary, interrupted light avertin anaesthesia and counteracted the cardiac and respiratory depression. Mörl gave 3 c.cm. intravenously. If the anaesthesia is deep the injection of coramine, while helping the general condition, permits of the operation being carried on without further anaesthetic being given.

More recently benzedrine sulphate has been tried by Michelsen and Verlot (1939). They found that animals were protected from the deleterious effects of a lethal dose of avertin by the use of a preliminary intramuscular injection of benzedrine sulphate and that benzedrine given after avertin shortens the anaesthesia by about 50 per cent. They tried the drug in man in five cases, and report that, given 0.08 to 0.09 gramme of avertin per kg. of body weight and subsequently 20 mg. of benzedrine sulphate, the patients "opened their eyes, reacted readily to pain stimuli, gave clear answers, followed commands.