THE USE OF ALUM-PRECIPITATED TOXOID IN DIPHTHERIA IMMUNIZATION

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Hitherto it has not been practicable to make use of routine diphtheria immunization on a large scale in rural communities on account of the number of injections of immunizing agent which have been necessary. The introduction of alum-precipitated toxoid has rendered it possible to immunize with one injection only—provided that the claims made on its behalf are substantiated.

With a view to proving its worth, a fairly large-scale experiment was made in the Haslemere Urban District and in the Ash and Normandy Parish of the Guildford Rural District. Both of these districts are essentially rural in character—Haslemere with a population of 9,290 and an area of 5,945 acres, Ash and Normandy with 7,292 people and 6,324 acres. The school population in each, with which alone I am here concerned, is about 900 to 1,000.

My reasons for selecting these districts need be but briefly stated. Haslemere is especially likely to suffer invasion by infectious disease on account of the large number of summer visitors, whilst it is also one district complete in itself and not too extensive for adequate treatment. Ash and Normandy is a locality that has, in the past, given considerable anxiety on account of the number of cases of diphtheria and diphtheria carriers, whilst the sanitary conditions of the area lend themselves

in unusual degree to the spread of diphtheria. For many reasons it is preferable for the medical officer of health to carry out the treatment personally rather than to relegate it to general practitioners.

Technique Used

Briefly, the method adopted was as follows. The parents of all children attending schools in the areas selected were invited to allow their children to be immunized and subsequently Schick-tested. Some 70 per cent. accepted, although a great many later refused to submit to the Schick test. In all, some 1,160 children were treated, mainly between the ages of 5 and 14, and 837 were Schick-tested 59 to 105 days later. Refusal to submit to more than one hypodermic injection is general, and constitutes one of the most cogent reasons for using a one-injection method of inducing immunity.

The material used was supplied by Messrs. Parke, Davis and Co., and by Messrs. Evans Sons Lescher and Webb Ltd., the dose of the former being 1/2 c.cm. and of the latter 1 c.cm. In all cases individual phials were used, although this added considerably to the cost of treatment. The most discussed aspect of the use of alum-precipitated toxoid is that of reactions produced by the initial injection. It may be stated at once that I am entirely satisfied with the small proportion of reactions and with the relatively trivial nature of such as did occur.

The site selected was just above the olecranon on the left arm, and all injections were made subcutaneously. After four or five days a very small subcutaneous lump developed at the site of injection on a large number of children, and persisted for some weeks. Many showed

Diphtheria Immunization and Schick Testing, Guildford Rural and Haslemere Urban Districts. Summary of Results

Ages in Years	Diphtheria Immunization								Schick Testing												Percentage of Success	Totals					
	Parke, Davis		Evans		Not Re- corded		Totals		Parke, Davis				Evans				Not Recorded					Totals				Children Immu- nized	Children Schick- tested
	Results		Results		Results		Results		Results				Results				Results					Results					
	No.	Reactions	No.	Reactions	No.	Reactions	No.	Reactions	No.	Neg.	Pos.	Pseudo	No.	Neg.	Pos.	Pseudo	No.	Neg.	Pos.	Pseudo		No.	Neg.	Pos.	Pseudo		
1	1	—	—	—	—	—	1	—	1	1	—	—	—	—	—	—	—	—	—	—	1	—	—	103.00	1	1	
2	1	—	2	—	—	—	3	—	1	1	—	—	—	—	—	—	—	—	—	—	1	—	—	100.00	3	1	
3	2	—	—	—	1	—	3	—	2	2	—	—	—	—	—	—	—	—	—	2	—	—	100.00	3	2		
4	10	—	7	—	2	—	19	—	5	5	—	—	6	5	1	—	—	—	—	10	1	—	90.99	19	11		
5	62	—	41	—	12	—	115	—	31	30	—	1	28	26	1	1	6	6	—	—	62	1	2	98.46	115	65	
6	57	—	42	—	14	—	113	—	36	33	2	1	26	22	3	1	9	8	—	1	63	5	3	92.95	113	71	
7	62	—	67	—	12	—	141	—	38	33	4	1	51	47	4	—	7	7	—	—	87	8	1	91.66	141	96	
8	51	—	62	—	2	—	115	—	39	38	1	—	49	42	4	3	1	1	—	—	81	5	3	94.38	115	89	
9	57	—	75	—	5	—	137	—	36	36	—	—	61	51	8	2	4	4	—	—	91	8	2	92.08	137	101	
10	50	—	76	1	4	—	130	1	35	32	2	1	54	43	9	2	3	2	1	—	77	12	3	86.95	130	92	
11	53	1	72	1	2	—	127	2	37	34	2	1	51	43	4	4	1	1	—	—	78	6	5	93.26	127	89	
12	51	—	60	1	5	—	116	1	38	34	2	2	52	39	11	2	4	4	—	—	77	13	4	86.17	116	94	
13	41	2	70	1	3	—	114	3	33	29	4	—	39	33	6	—	3	3	—	—	65	10	—	86.66	114	75	
14	8	1	13	—	2	—	23	1	1	1	—	—	3	1	—	2	1	1	—	—	3	—	2	100.00	23	5	
Not known	—	—	3	—	—	—	3	—	—	—	—	—	1	1	—	—	1	—	1	—	1	1	—	50.00	3	2	
Totals	506	4	590	4	64	—	1,160	8	333	309	17	7	421	353	51	17	40	37	2	1	699	70	25	Average 91.18	1,160	794	

Of the 1,160 children immunized, the parents of 161 of these refused to agree to their children being Schick-tested.

In addition, a number of children were immunized but left the school or district before the Schick testing was carried out.

An additional twenty-nine children were Schick-tested, but owing to their absence from school on the date of the inspection of Schick results it is not possible to record this group as "negative," "positive," or "pseudo."

Of the seventy children who were positive after Schick testing, fourteen were re-tested, resulting in seven being negative and seven remaining positive.

From the above notes it will be seen, therefore, that the actual Schick tests carried out number 837—that is, 794 + 29 + 14.

The results do not, to me, seem fair to Messrs. Evans Sons Lescher and Webb Ltd., because they include the school which showed such abnormally poor results—twenty positives out of 136 tested.

slight tenderness, but of so trivial a nature that the children had not themselves noticed it until questioned and specially examined for it. These cases have not been included under the heading of reactions because there was nothing to give cause for complaint by children or parents, nor was there any interference whatever with work or play.

The table shows the number of cases giving reactions of a more severe degree, where complaints of swelling or pain were volunteered. One of these appeared to be a small haematoma due to the puncture of a small vein, and ought strictly to be discounted. In most there was a tender and somewhat painful lump varying from the size of a pea to that of a half walnut, and accompanied, frequently, by slight reddening of the skin and, in rare cases, by slight oedema. *In no case was there any constitutional disturbance.* In fact the symptoms were no worse than those occasioned by an accidental knock on the elbow. The symptoms developed on the third day, reaching their maximum on the fifth day, and thereafter subsided gradually over a period of a week. Reactions were more numerous in older children, none at all occurring below the age of 10. I was particularly struck by the prevalence of reactions amongst overgrown and over-developed children, such as appear much older than their actual years. This is interesting in view of my experiences with adults recorded later. The most severe reactions were in children of 12 to 14 years.

Although immunity is presumed to develop within forty-two days, Schick testing was delayed for a minimum period of nine weeks after treatment in order to give every opportunity for a fair test. Of the number of children treated, 72 per cent. were later Schick-tested. The remaining 28 per cent. were either absent from or had left school, or refused to submit to a further injection. Readings were taken on the fourth or fifth day after testing, and in many cases on several consecutive days between the third and seventh.

Results

The results are tabulated to show the measure of success at different ages and with each firm's product. As many as 91 per cent. of the children appear to have been successfully immunized.

The immunizing agent used and marked "Not Recorded" was almost certainly entirely that of Parke, Davis and Co., since approximately equal numbers of children were done with each firm's product. The most striking lesson from the results tabulated above is undoubtedly the complete absence of reactions in children below the age of 10 years, accompanied by a relatively high percentage of successful results. Of the 437 children immunized not one showed any reaction, and 93.6 per cent. were Schick-negative. Of the seventy positive reactions only three were of the usual strongly marked type. Most of the others were exceedingly faint, and in artificial light would certainly have been missed. Every doubtful case was labelled positive.

In one particular school the number of Schick-positives was so large (twenty out of a total of 136 treated) that it was felt that sufficient time had possibly not been allowed to permit of the development of immunity. Accordingly, fourteen of these were re-tested at the end of a further period of five weeks. In seven—that is, 50 per cent.—of these, the positive reaction had become negative. (These results are not included in the table.) Apparently, in some cases only a partial immunity is produced, and either a larger dose of toxoid should be used, or else a stronger concentration of toxin used for the Schick test, in order that these partial failures may be more definitely revealed. It is possible that some cases show a very delayed response to the immunizing agent.

It may be of some significance that this particular school is one which has, during the past year, given a remarkably large number of cases of diphtheria and of carriers, mostly of a type peculiarly resistant to treatment. In any case, it seems that a larger interval between immunization and Schick testing would make the percentage success of this treatment appreciably higher.

Treatment of Adults

A brief note on the results obtained in treating a small number of adults is of interest.

The total number immunized is only seventeen. Of these, two showed reactions of a severe though not alarming character. In each case symptoms developed on the third day, reached a maximum on the fifth, and thereafter subsided during the following week or so. Both of the individuals were undoubtedly of an especially unsuitable type for experimental treatment of any kind, one in particular being highly introspective, subject to asthma, nettle rashes, and chronic mild invalidism. Both of these persons had some constitutional reaction, of the nature of a cold in the head, with temperature mounting to 100° or 101° F., accompanied by a painful lump at the site of inoculation, oedema, and reddening of the skin of the arm. All adults treated were found to be Schick-negative on subsequent testing. As a result of these cases all adults were subsequently treated by two doses of T.A.F.

An experiment was made by administering two small doses of alum-precipitated toxoid, at intervals of one week, 1/10 c.cm. only being used on each occasion. The number of reactions, and the severity of them, was so noticeably more than by the single-dose method that this was given up after treating just over 100 cases.

Planning of an Immunization Scheme

It is realized that the immunization of a school population such as I have just described is, by itself, of no permanent value. A scheme for continued annual treatment of all in-coming children must be put into operation in order to preserve an immune population. In settling the details of such a scheme, regard must be paid to practical possibilities rather than to the ideals one would like to aim at.

The handing over of all immunizations to private practitioners is open to many objections. In addition to the extra expense involved, it is undoubtedly better that the whole scheme should be operated by one individual rather than by an untold number of practitioners, many of whom may have had no experience of Schick testing, and whose results in any case may vary individually. It becomes absolutely essential to reduce the number of visits necessary per patient to the minimum. For that reason preliminary Schick testing must be dispensed with entirely. Alum-precipitated toxoid has the great advantage of eliminating all but one injection, and will in future be used except for adults and for those children over 12 years of age whose maturity leads to the expectation of reactions similar to those in adults.

It is desirable that children should be protected against diphtheria before they attain school age. There is the added advantage that, from the results I have obtained, reactions are few or absent, and that the percentage of success is apparently at its optimum. In future, it is hoped to introduce a scheme for the immunization of children attending infant welfare centres, and all commencing school at the age of 5.

Conclusion

I am aware that it is generally held that Schick testing subsequent to immunization should be invariably performed. Admittedly it is a policy of perfection, but in widespread rural districts the subsequent two visits involved, and the time occupied by them, render it extremely difficult, or possible only at the expense of a reduction in the scope of the treatment. It seems to

me much wiser to perform immunization in all schools, and to recognize and accept the fact that some 5 to 8 per cent. of children may remain susceptible. It is surely preferable to have only this small percentage of susceptibles throughout the whole district rather than patches of complete immunity and patches of complete untreated susceptibility. From time to time selected schools will be Schick-tested in order to exercise some check on the results obtained, but whereas it is hoped to immunize some thousand children annually, only one-fifth of these may be subsequently tested.

I question also absolute reliance upon the result of the Schick test. There is no proof that any one negative result represents a *permanent* immunity. It may be affected by other factors at present unknown, just as the Wassermann reaction may be affected by drugs or illness. Indeed, I have a record of one boy admitted to hospital with a severe attack of diphtheria who had been found Schick-negative barely four weeks previously, and who had on that account, presumably, not been immunized.

The total cost of the treatment has been rather less than 2s. 6d. per head. If bulk bottles of alum-precipitated toxoid had been used this would have been reduced to very little more than one shilling.

Every child has been supplied with a certificate stating the treatment given and the result of the Schick test. This should prove of importance in later life and in the event of removal to other districts.

Alum-precipitated toxoid has been used in three or four closed institutional populations in this district. The results in every instance have been exactly analogous to those recorded above. In every case treatment has been completely successful in stamping out endemic diphtheria, and no person who has received one injection of alum-precipitated toxoid has developed diphtheria.

PREVENTION OF DIPHTHERIA BY THE "ONE-SHOT" METHOD USING ALUM-PRECIPITATED TOXOID

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Recent studies have materially increased our knowledge of the various factors which enter into the creation and development of immunity. As the interest which medical officers of health take in the subject of diphtheria is largely that which concerns the preventive aspect, so this paper deals with the chemico-immunogenic substance alum-precipitated toxoid (A.P.T.), in respect to its effects on a number of children on whom it was tried out.

The material for the investigation consisted of 370 children in three residential institutions. The table given below shows the percentage of positive reactors. An interesting feature is the high number of positive reactors in Institution C. A rational explanation of this lies in the fact that there was no diphtheria in this sheltered community for several years.

Institution	No. of Children Schick-tested	No. of Schick-positive Children	Percentage of Positive Reactors	Average Age of Children
A	182	55	30	12½ years
B	112	35	31	11½ years
C	76	40	53	10½ years

All the Schick-positive children were given 1 c.cm. of A.P.T. by deep subcutaneous injection. (The Moloney test was not applied, as this work is the preliminary of a large-scale immunizing campaign in which it is the intention not to do the Moloney test if it is safe to do without it.) The following table clearly demonstrates the high immunogenic properties of this substance, as determined by its ability to convert positive reactors to negative two months after its administration.

Institution	No. of Schick-positive Children given A.P.T.	No. of Children Schick-negative 2 Months after A.P.T. Injection	Percentage Conversion (approx.)
A	55	53	95
B	35	31	90
C	40	37	93

Reactions Encountered and Results

These fell into four groups. (1) The commonest reaction (almost universal) was that of a small painless induration at site of injection, approximately the size of a pea. (2) Diffuse erythema extending, approximately, around an area of three inches from site of injection was present in 10 per cent. of those injected. (3) Brawny induration, with hyperaemia over practically the whole arm, with stiffness in joints and local heat, was present in six cases and took six days to go back. (4) In one case there was a minute sterile abscess at the puncture site. In view of the fact that 84 per cent. of all the children injected were over 10 years of age, the reactions were surprisingly light, and the few that were marked were in the older children.

As to the reliability of the preparation 90 to 95 per cent. of the children have been rendered Schick-negative. This shows definitely its high conversion power. There has been no reaction of sufficient severity to warrant apprehension. Indeed, the reactions have been of such a comparatively mild nature that the doctors engaged on this work with us have expressed a desire to carry out large-scale campaigns in other districts, using the same material. In addition, the procedure is less time-consuming, and the failure-to-turn-up-for-second-injection bugbear does not exist.

If reactions could be rendered less severe without impairing efficiency we believe that we would then be in the possession of an ideal agent for immunization.

Conclusion

Our conclusion is that (a) A.P.T. is, as indicated by the variant, the Schick test, an immunizing agent against diphtheria of very high degree; and (b) in our experience it is quite safe to use in children under or over 10 years of age, subject, of course, to the limitation that it may cause a brisk reaction. The object of this presentation has been achieved if the attention of workers in this field is obtained, so as to elicit their experiences as regards (1) the necessity of a Moloney test, (2) any very severe reactions met with, and (3) the percentage of "converts" obtained with A.P.T.

The materials used in this work were supplied by Burroughs Wellcome and Co.

We have received the first issue, published at Rosario last June, of a new Argentine quarterly, entitled *Anales de Cirurgia*. The issue contains exclusively original articles, among which may be mentioned those on treatment of gastric and duodenal ulcer, neurofibromas and schwannomas, lympho-epithelial cysts of the neck, intra-venous cholecystography and affections of the gall-bladder (Victor Putti), and renal carbuncle.