AN EVALUATION OF MODERN DIPHTHERIA PROPHYLACTICS

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The investigation described below was prompted by reports in American literature of successful immunization of children against diphtheria with potent toxoid preparations administered in less than the three customary 1 c.cm. injections. The experiment was rendered possible by the courtesy and kindness of Dr. R. A. O'Brien, director of the Wellcome Research Laboratories, who supplied the whole of the materials with which it was carried out.

Aim and Method of Investigation

The primary object of the investigation was to compare the percentage of children rendered Schick-negative in two similar groups, when one was given a course (2 c.cm.) of a potent formol-toxoid (F.T.) and the other 2 c.cm. of an alum-precipitated toxoid (A.P.T.). As a preliminary each child in both groups was Schick- and Moloney-tested, a 1 in 200 dilution of formol-toxoid being employed for the latter purpose. The posterior Schick test (with a control in every case) was performed four weeks after the last prophylactic injection had been given.

The experimental material was drawn from two residential institutions (contributing respectively 109 and 213 children), nine smaller homes (ninety-eight children), a hospital for rheumatic children (fourteen children), and two elementary schools (185 children), while twenty-three children convalescent from scarlet fever or measles were also included, giving a total of 642 children.

For the purposes of the experiment it was disappointing that so many of the children (424) proved originally Schick-negative, a disadvantage, nevertheless, to be expected in conducting investigations of this kind in residential institutions, which are otherwise particularly suitable for the purpose. The experimental group was further attenuated by the relatively high proportion of children found to be sensitive to formol-toxoid on Moloney testing. These children were, however, not entirely eliminated from the investigation, which was accordingly broadened to include a group of "Schick-positive Moloney-positive" children, who were given a full course (3 c.cm.) of toxoid-antitoxin floccules (Burroughs Wellcome and Co.), the children so treated being similarly Schick-tested four weeks after receiving the final prophylactic injection.

The fact that the number of children originally found to be Schick-positive does not quite correspond with the number retested is due to a variety of unavoidable causes—for example, children being discharged from the institutions in the interim, non-institutional children leaving the town, or, more commonly, failing to attend for retest at the correct interval, and so on.

After preliminary Schick and Moloney testing the children were classified as follows:

TABLE I

	Numbers	Per cent.
Schick-positive, Moloney-negative ...	164	25.5
Schick-positive, Moloney-positive ...	54	8.4
Schick-negative, Moloney-positive ...	227	35.3
Schick-negative, Moloney-negative ...	197	30.6
Totals ...	642	99.9

It will be seen that, so far as the administration of potent toxoid preparations was concerned, the experimental group was reduced to 164 as a consequence of these tests, although fifty-four Schick-positive children were left to be immunized with toxoid-antitoxin floccules (T.A.F.).

The graph below shows the susceptibility of the children in successive age periods to Schick toxin, and to a 1 in 200 dilution of formol-toxoid administered intradermally (Moloney test). The high degree of susceptibility to Schick toxin at an early age, falling to a low level at the other end of the age scale, is in sharp contrast to the low degree of sensitiveness to formol-toxoid in infancy, steadily rising to a very high level in adolescence.

Graph showing susceptibility at different age periods to
(a) Schick toxin, (b) 1 in 200 dilution of formol-toxoid.

The fact that sensitiveness to formol-toxoid occurs to an appreciable extent in quite young children, at any rate in Cardiff, is perhaps better shown by Table II, which sets out the results of Moloney testing (using a 1 in 200 dilution) 873 unselected children—that is, a group of 231 in addition to the 642 tested in this investigation.

TABLE II.—Sensitiveness to Formol-toxoid (1 in 200 dilution)

Age Group	Tested	Positive	Positive Per cent.
0 to 2 years ...	14	1	7.14
2 to 4 " ...	83	8	9.63
4 to 6 " ...	129	20	15.50
6 to 8 " ...	121	23	19.00
8 to 10 " ...	154	56	36.36
10 to 12 " ...	153	72	45.57
12 to 14 " ...	140	79	53.42
14 to 16 " ...	58	36	62.06
16 to 18 " ...	16	12	75.00
Total ...	873	307	35.15

These figures suggest that a preliminary Moloney test is desirable even in children under 8 years of age, if it is proposed to immunize them with the more potent toxoid preparations. This conclusion is further strengthened by experiences with the stronger dilutions of formol-toxoid (1 in 100, 1 in 50, 1 in 20 dilutions) referred to below.

The alum-toxoid employed (serial number B 8725) was a precipitated toxoid (A.P.T.), and was at first very cautiously administered, as it had at that time (February, 1934) not previously been used on human beings. In the first batch of twenty-one children the dose employed, therefore, was 0.1 c.cm., which was followed a week later by 0.25 c.cm. in those showing no reactions, 0.65 being given two weeks later, and a final dose of 1 c.cm. a fortnight afterwards. It will be seen that with this procedure the full course of A.P.T. was 2 c.cm. When more experience of A.P.T. had been gained, an initial dose of 0.5 c.cm. was given, followed by a similar dose in a week and 1 c.cm. two weeks after the second injection. Later still 1 c.cm. was given in each of two injections at an interval of two weeks. No child received more than a total of 2 c.cm. A.P.T., and the posterior Schick test was carried out in all cases four weeks after the final injection of prophylactic. The potent formol-toxoid (B 8553) was given mainly in two injections of 1 c.cm. at fortnightly intervals, but some children who showed reactions after the first 1 c.cm. received the second in two instalments of 0.5 c.cm. in successive weeks. Here also the posterior Schick test was performed four weeks after the final injection.

The smaller "Schick-positive Moloney-positive" group were given three 1 c.cm. injections of toxoid-antitoxin floccules (Burroughs Wellcome and Co.) weekly, and were posterior Schick-tested four weeks after the last injection.

Table III shows the results obtained.

TABLE III.—*Evaluation of Efficiency of Prophylactics*

Nature and Amount of Reagent Used	Number of Schick-positive Children Immunized	Number of Immunized Children Posterior Schick-Tested	Number Positive on Posterior Schick Test	Number Negative on Posterior Schick Test	Per cent. Immune on Posterior Schick Test
Alum-toxoid (2 c.cm.)	78	75	17	58	77.3
Formol-toxoid (2 c.cm.)	86	76	9	67	88.1
Toxoid-antitoxin floccules (3 c.cm.)	39	36	6	30	83.3
Total ...	203	187	32	155	82.8

In addition to the children receiving a straightforward course of A.P.T., F.T., or T.A.F., there were nine children who, after an initial dose or doses of either A.P.T. or F.T., were subsequently changed to T.A.F., because of local reactions caused by the toxoid. Seven children received one dose of A.P.T. followed by two of T.A.F., and all of these were Schick-negative four weeks after the last injection of T.A.F. Two children received one dose of F.T. followed by two of T.A.F., and one of these was positive and the other negative on retest four weeks after the last injection. Five children who received only two injections (each 1 c.cm.) of T.A.F. were all positive when Schick-tested four weeks after the last injection.

Local Reactions

No general reaction was observed amongst any of the children treated. Local reactions of varying degrees of intensity were seen, especially following injections of A.P.T., and, as shown in the table below, a very few of these were associated with slight induration, which, however, in no case persisted. No abscess formation was encountered. The local reactions consisted in the main of areas of erythema, varying from one inch to four inches in diameter. In all cases the local reaction was transient, and had disappeared in a week or ten days after the injection.

TABLE IV.—*Local Reactions*

Reagent	Number Treated	Number Showing Reactions	Number Showing Induration	Per cent. Showing Reactions
A.P.T.	85	50	5	58.8
F.T.	88	19	5	21.5
T.A.F.	53	12	2	22.6

The ages of the children in whom reactions were noted are shown in Table V.

TABLE V.—*Age Incidence of Local Reactions*

Age in years	A.P.T.	F.T.	T.A.F.
1 year	0	0	0
2 years	2	0	0
3 "	5	2	0
4 "	4	3	0
5 "	5	1	0
6 "	4	3	0
7 "	3	0	0
8 "	6	2	0
9 "	8	2	0
10 "	2	2	0
11 "	3	4	0
12 "	2	0	1
13 "	4	0	6
14 "	0	0	2
15 "	0	0	1
16 "	2	0	2
Totals ...	50	19	12

It should be made clear that the age grouping of the children immunized with A.P.T. and F.T. was identical. A relatively larger number of older children were immunized with T.A.F. (owing to the increased sensitiveness to toxoid encountered at these ages), but at least half of the children receiving T.A.F. were under 10 years of age. It will be observed that, whereas the tendency towards local reactions is with the toxoid preparations pretty evenly distributed over all ages from infancy to adolescence, reactions obtained with T.A.F. were confined to children over 12 years. It should also be borne in mind that the toxoid prophylactics were given only to Moloney-negative children, so that the number and degree of local reactions observed in this investigation furnish no guide as to the incidence and severity likely to be encountered with toxoid preparations among the general school population.

Features of Special Interest

Although it would be unwise to draw any general conclusions from so small a series of observations, certain suggestive features merit comment. The very high degree of immunity found to exist four weeks after the last injection represents a distinct advance, and brings active immunization definitely within the scope of practical measures, in the control of actual outbreaks of diphtheria in the community, whereas the more slowly acting prophylactics of the past could hardly be relied upon in this connexion. The differences in efficiency of the three prophylactics tested are not great, but, such as they are, the advantage would seem to lie with formol-toxoid. The alum-precipitated toxoid employed seemed to be very prone to evoke local reactions, which, though not alarming, would certainly militate against the success of an immunization scheme for the general community.

One great drawback to the general employment of formol-toxoid is the need for a preliminary Moloney test, which means yet another intradermal injection, and an extra visit for inspection purposes in addition, as the Moloney test is best read at forty-eight hours.

One way, possibly, of eliminating this extra visit of inspection at forty-eight hours which was considered, a Dr. O'Brien's suggestion, was the use of 1 in 100 or 1 in

50 dilutions of formol-toxoid for the intradermal test of susceptibility to toxoid. By thus increasing the amount of toxoid injected, it was hoped to produce a more lasting local reaction, which would be discernible a week later, when the final reading of the Schick test is due.

Fifteen children, aged from 2 to 10, were accordingly given 0.2 c.cm. of a 1 in 100 dilution of formol-toxoid (B 8706). Two (aged 2 and 5 years respectively) were positive, but the reaction quickly faded after forty-eight hours. Nine nurses (aged 18 to 25 years) were then tested, and, as expected, seven of these gave very definite reactions, but only in five of these was the reaction discernible at the end of the week. Eighteen children (aged from 5 to 14) were then given 0.2 c.cm. of a 1 in 50 dilution of formol-toxoid (B 8707) intradermally. Thirteen were negative, but of the five who gave a positive reaction in only three was the reaction discernible a week after the test.

It is obvious that increasing the strength of the formol-toxoid does not solve even one of the difficulties arising out of the employment of the Moloney test.

A trial was next made of a method which aims at facilitating the immunization of children with formol-toxoid without the need for a preliminary intradermal test. By this system—which Dr. O'Brien calls the "universal or detector dose" method—all children at their first visit are given subcutaneously a small dose, say 0.05 c.cm., of formol-toxoid made up to 1 c.cm. in saline. This minute dose of toxoid might be expected to cause a recognizable reaction in those who are sensitive, but it was thought that this reaction would not be severe enough to prevent its universal application as a detector dose. Children negative to the detector dose would receive two full doses of 1 c.cm. of potent formol-toxoid later, whereas those showing some reaction could be immunized, either by a series of small doses of formol-toxoid spread over a long period, or, more rapidly, by two doses of T.A.F. By this system immunization of insensitive children with formol-toxoid could be completed in the usual three visits. Eighteen children (aged from 3 to 14) were dealt with in this way. Thirteen children showed no reaction of any kind after the "detector dose," but five children showed marked local reactions, and two of these (aged 7 and 9 years) gave general reactions as well, both having temperatures of 100.6° F. for a brief period. It is obvious that for the age group over 5 years, at all events, this method has its limitations.

Conclusions

It would seem, then, that where a routine Moloney test cannot be conveniently employed the prophylactic to be used should be T.A.F., which this series of observations suggests is only slightly inferior in efficiency to toxoid preparations, and which, in my hands, has never produced a local or general reaction in a child of 10 years or under.

For institutional work, where Moloney testing is possible, formol-toxoid would seem to be the prophylactic of choice, and the above observations indicate that a high percentage of successes can be obtained with this antigen (in four weeks) after a course of two injections.

In this experiment the alum-toxoid preparation used did not compare favourably with formol-toxoid, or even with toxoid-antitoxin floccules, and its tendency to produce local redness is a contraindication to its general use outside institutions.

I wish to record my grateful thanks to my former colleagues, Dr. C. W. Anderson, Dr. Jean W. Smellie, and Dr. J. D. Spillane of the Cardiff Public Health Department, who helped with some of the testing and immunizations above referred to. I must acknowledge also the very great assistance given, in a variety of ways during this investigation, by the Epidemic Officer of that department (Mr. F. Davey).

TREATMENT OF BED-SORE WITH ELASTIC ADHESIVE PLASTER

BY

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The following method of treatment of bed-sore has, in my practice, shortened the time of healing, lessened the labour of the attendant, and diminished the need for skilled nursing. It has been tested in a total of ten cases, in one of which sixteen weeks' treatment with the usual remedies had failed to improve the condition.

Two pieces of elastic adhesive plaster, one over the other, are applied so that the bed-sore and the skin surrounding it for at least an inch are covered. If the bed-sore has a greater diameter than the elastoplast bandage two pieces may be laid side by side and held together by two other pieces placed at right angles. The elastoplast is left in position as long as it will adhere—usually, in the early stages when discharge is plentiful, twelve to forty-eight hours. It is then replaced by similar pieces of adhesive plaster, and this is repeated until healing is complete. On removal of the bandage no attempt should be made to clean the surface of the sore; it suffices to wipe away the discharge from the surrounding skin with cotton-wool or soft cloth before applying a new piece of bandage. Elastoplast was used in the following cases.

Case I

A man, aged 72, with left hemiplegia, had a bed-sore two and a half inches in diameter on the left buttock. Acriflavine gauze dressings were applied to the ulcer, and the surrounding skin was treated with methylated spirit and powder (starch, zinc oxide, and boric acid). At the end of five weeks the ulcer was almost three and a half inches in diameter. A well-padded tow-ring placed round the ulcer to release the pressure had to be abandoned in less than a week because of discomfort. During eleven subsequent weeks B.F.I. powder was used instead of acriflavine. Extra powder was dusted on according as the surface became moist, and the whole was cleaned off gently every morning. The ulcer did not increase in area, but the edges became raised and unhealthy-looking.

Elastoplast was then tried. The first dressing remained on for about thirty hours; on removal the ulcer base was pink, and its edges were flat and clean. Elastoplast was reapplied four times at lengthening intervals, and on the twelfth day the site of the ulcer was covered with firm skin. Methylated spirit and dusting powder were used twice daily thereafter. There was no return of the bed-sore. Pulse rate and temperature were normal for the duration of the elastoplast treatment.

Case II

In this case, that of a woman, aged 86, who had gangrene of the right foot and was delirious each night, a bed-sore on the left buttock about three inches in diameter had been treated for five days with an ointment containing zinc oxide, castor oil, and tinct. benzoin. co., without improvement. Elastoplast was applied on the sixth day, and healing was complete seven days later, although the patient was steadily losing ground.

Case III

A woman, aged 63, with rheumatoid arthritis, had a bed-sore about one inch in diameter over the lower end of the sacrum. The usual remedies had been used for about a week with little benefit. Elastoplast treatment was then instituted, and resulted in cure of the sore in five days.

The patients in these cases were cared for night and day by experienced and fully qualified nurses. Seven other patients, having various primary disorders, were treated for bed-sore with elastoplast, but nurses were not in attendance. The time taken for healing was from seven to fifteen days. There was no increase in temperature, and the pulse rate was always below 100. (Case II was