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PERSISTENCE OF ANTIBODY IN ADOLESCENTS AND ADULTS AFTER A THIRD, BOOSTER, DOSE OF POLIOMYELITIS VACCINE

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In previous reports (Reports, 1958, 1959) results were given of the neutralizing antibody responses obtained in a group of public-school boys and medical personnel after immunization with inactivated poliomyelitis vaccine. The subjects, none of whom had detectable antibodies to any of the three types of poliovirus before immunization, were given two injections of vaccine four weeks apart and a third, booster, injection 6 to 12 months later; serum samples were taken two weeks after the third dose. Further tests have now been made with the same group to determine the persistence of antibody after periods of up to two years.

Methods

Samples of serum were obtained from 46 of the schoolboys and from eight of the medical personnel at 18, 21, or 24 months after the third dose. They were titrated for neutralizing antibody in parallel with the serum samples taken two weeks after the third dose, all sera being tested against each virus type at one time. The galactose colour test was employed (Perkins and Evans, 1959), using fourfold serum dilutions in 0.25-ml. amounts, mixed with 100 TCID₅₀ of virus in 0.25 ml. All dilutions were made in Hanks solution and two cell-culture tubes were used for each serum dilution. Titres are expressed as the reciprocal of the initial dilution of serum protecting 50% of the tubes from virus action.

A fourth dose of 2 ml. of vaccine was given to those subjects whose antibody to type 1 had fallen to an undetectable level. The antibody responses to this dose were determined two weeks later.

At the time of taking the serum samples, saliva was obtained from some of the boys. After incubation at 56° C. for 30 minutes, 0.25 ml. of the twofold and eightfold dilutions were mixed with 10–30 TCID₅₀ of virus and, after 3½ hours' incubation at 37° C., added to prepared monkey-kidney-cell cultures, two tubes being used for each salivary dilution. Microscopical readings were taken after four days' incubation, as by this time the tubes had become acid.

Results

Figs. 1, 2, and 3 show the decline in serum antibody to each of the three types after the third dose of vaccine. After 18 to 24 months all 54 subjects had detectable

FIG. 1.—Decline in type 1 antibody titre after a third dose of poliomyelitis vaccine.

FIG. 2.—Decline in type 2 antibody titre after a third dose of poliomyelitis vaccine.

FIG. 3.—Decline in type 3 antibody titre after a third dose of poliomyelitis vaccine.

antibody to types 2 and 3 poliovirus, 44 showing titres of 128 or more to type 2, and 46 to type 3. However, 29 had type 1 antibody titres of 65 or less, and in nine of these antibody was undetectable at a titre of 4 and, on retitration, at a titre of 2.

These results can be related to the responses to the two primary cases and to the third dose of vaccine. Almost all 54 subjects had, at the time the third dose was given, measurable antibody to types 2 and 3 induced by the primary course and had responded well to the third dose. With type 1, however, 22 subjects had lost their antibody by the time the third dose was given and, compared with those who still had antibody, had tended to respond poorly to the third dose. The titres of those 22 subjects are shown in Fig. 1 by large circles, and it is evident that the antibody levels at 18 to 24 months are much lower—all being 32 or less and including eight of less than 2—than those of the other 32 who had had detectable antibody at the time the third dose was given. Of these 32 only four had titres of 32 or less, including one with no detectable antibody. It is interesting that the four with low titres had all shown poor responses to the third dose and before this injection had had very low titres (2), which may have been due to serum inhibitors rather than to true poliomyelitis antibodies.

Though individuals lost antibody at different rates, it can be seen that, in general, the higher the response two weeks after a third dose the higher the titre 18 to 24 months later. The decline of titre in a few individuals was small, while with others it was considerable.

Table I gives the geometric mean titres two weeks and 18 to 24 months after the third dose and the differences between the two. In general, the drop after 18 months was less than after 21 to 24 months. It was greatest in the 21-months group, whose mean response to the third dose was higher than that of the other groups. The average decreases in titre for all the subjects were similar for the three types, ranging from 76% for type 2 to 81% for type 1. Those subjects without detectable antibody were excluded from this calculation as their fall could not be determined.

The eight subjects who had lost their type 1 antibody after the primary course and also after the third dose did not respond well when given a fourth dose of vaccine. In six, the responses were definitely poor, all being less than 128, and in the other two only moderate—128 and 512. All eight subjects, however, responded satisfactorily to types 2 and 3, having titres ranging from 512 to 8,192.

There was no evidence, from the antibody levels obtained, that any of the subjects were naturally infected by any of the poliovirus during the period of this study.

TABLE I.—Geometric Mean Antibody Titres of Groups of Schoolboys and Adults Two Weeks and 18 to 24 Months After a Third Dose of Poliomyelitis Vaccine

Type	Titres at:				% Decrease in Titre	
	2 Weeks	18 Months	21 Months	24 Months	By Groups	For all Subjects
1	224 812 425	61	108	74	73 87 83	81
2	944 1,560 676	257	287	186	73 82 73	76
3	720 3,780 870	257	644	178	64 83 80	77

Of the samples of saliva tested for antibody to poliomyelitis virus, only 1 out of 21 inhibited type 1 virus, 4 out of 31 inhibited type 3, and none out of 25 inhibited type 2. None of the positive samples neutralized virus at a dilution of more than 4 and were from subjects with homotypic serum antibody titres of at least 2,048.

Discussion

It is evident from these results that the persistence of antibody and the level maintained after a third dose of poliomyelitis vaccine were dependent on whether detectable antibody was present at the time of the third dose, and this in turn depended on the potency of the vaccine used for the initial two doses (Salk, 1958; Kendall *et al.*, to be published). The vaccines used throughout these studies (Reports, 1958, 1959) were the best available to us, but in spite of this a proportion of subjects maintained detectable type 1 antibody levels for only short periods after the third dose, and even when given a fourth dose produced antibody responses which were similar to those which had been shown not to persist after the third dose.

The average fall in titre for all types after the third dose was from 76 to 81% in 18 to 24 months, and very similar to that found after natural infection by Lennette and Schmidt (1937). Their results indicated that, after type 1 infection, homotypic neutralizing antibody fell on the average to 25% of its peak value after a year, to 21.5% after 18 months, and to 18% after two years. The degree of fall during two years was negligible in some subjects, in others it was over tenfold. From our studies, as the number of subjects in each of the three groups are small, it was not possible to be certain if antibody declined after a booster dose at a constant date or decreased more slowly after an initial quicker fall. But mean titres at the three times of bleeding did seem to show that the average rate of antibody decline was not decreasing appreciably (Table I). The titres of some of the subjects had dropped very little over the study period and were similar to the examples given by Salk (1958), while a few had declined by as much as 12-fold. In the three groups of children studied by Salk, and who received vaccines of different potency, the average decline of antibody of each group during the year after a booster dose varied from a little over twofold to more than eightfold, and in those receiving poor vaccine a fifth had lost the type 1 antibody induced by the booster dose. All these findings indicate that antibody decline varies considerably from one individual to another.

Even if the subsequent average decline in antibody is somewhat slower than that occurring initially after infection or vaccination, it must be stressed that many subjects lose antibody very much faster than the mean. In determining vaccine schedules for the future these latter subjects are of most importance, as the intervals at which people should be given booster doses depend on how long they can maintain antibody in their circulations. Thus, if we presume that the average antibody fall found by us is continued, titres would reach, after an interval of about five years, a level of 1% of the post-third-dose titres (Fig. 4). In order to maintain detectable antibody and thus ensure that a fourth dose of poliomyelitis vaccine is effective when given after this interval—which is the interval adopted with other prophylactics (Wellcome Foundation, 1960)—titres of more than 100 for all three types should be attained after the third dose. At the present time, however, three doses of the better commercial vaccines are producing

in triple-negative subjects such titres to type 1 in only 70–75%, but to types 2 and 3 in almost 100%. This group of subjects accounts for at least half of all those paralysed and is the most difficult to immunize with inactivated vaccine.

The lowest titre found by us to be produced by natural poliomyelitis infection was 100; it was also the lowest titre after the third dose in the subjects studied here which ensured detectable antibody two years later or a good antibody response to the fourth dose, and the

FIG. 4.—Fall in antibody titre after a third dose of poliomyelitis vaccine.

lowest titre obtained from a third dose after the use for the initial injections of a vaccine of sufficient potency to give detectable antibody to all types in 95% of subjects at the time of the booster dose.

Until evidence is produced to the contrary, it must be assumed that killed poliomyelitis vaccine protects only as long as antibody remains in the circulation, and it is generally agreed that this is the object of vaccination (Wellcome Foundation, 1960). Thus, from the antibody results reported here, the protection afforded by the best commercial vaccines for a five-year period can be estimated after three doses and after a fourth given within two years of the third. These estimated values, which are consistent with the 90% protection being found in the field after three or more doses over a shorter period (Poliomyelitis Surveillance Report, 1959), are given in Table II and indicate that protection would probably be increased from 84 to 95% if four instead of three doses were given.

TABLE II.—Predicted Maximum Five-year "Protection" After Three and Four Doses of Inactivated Poliomyelitis Vaccine

	Type 1*		Type 2	Type 3	Predicted Five-year Protection as Judged by a Titre of > 100 to All Types
	A	B			
Distribution of paralytic cases by virus type in unvaccinated subjects	50	30	5	15	84%
Percentage of vaccinees with a titre of > 100 after 3 doses	72	97	100	94	
No. of paralytic cases prevented after 3 doses	36	29	5	14	
Percentage of vaccinees with a titre of > 100 after 4 doses	90	100	100	100	95%
No. of paralytic cases prevented after 4 doses	45	30	5	15	

* Subjects without (A) and with (B) type 2 antibody before infection or vaccination.

It is questionable whether the effort required to give a fourth dose, within a year or two of the third, to the community at large is justified by this increase in protection, especially in those who are regularly vaccinated with other prophylactics and who will be receiving poliomyelitis vaccine at the same time. It would probably be of more general value first to encourage those subjects who have had only one or two doses of vaccine to complete the full schedule of three doses. If, however, vaccine with more potent type 1 component can be made, consideration of a fourth dose shortly after the third would be unnecessary. With present vaccines, a fourth dose should be given to those at special risk or when increased protection is particularly desirable. In such cases the optimum vaccination schedule is two doses four to six weeks apart, a third six to nine months later, and a fourth six to nine months after the third.

The results given here were obtained in adolescents and in adults, in whom the primary vaccination course may be somewhat less effective than in children (Report, 1958). The conclusions drawn are perhaps on the cautious side for this age-group, but are applicable to the other age-groups who are now being offered vaccination against poliomyelitis.

Summary

A study in 54 adolescent and adult subjects showed that neutralizing antibodies to types 2 and 3 persisted at a much higher level than antibody to type 1 when tests were made 18 to 24 months after a third dose of poliomyelitis vaccine.

The persistence of antibody after the third dose was shown to be dependent on whether antibody induced by the two primary doses of vaccine was present at the time the third dose was given.

The relation of these findings to the efficacy of vaccination is discussed.

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"The fact is that the study of the causes and prevention of crime is in its infancy. We must learn as we go along. We are concerned not only with personal characteristics that make some people more prone than others to become delinquent. Our study must embrace also those elements of our society, products of our history, traditions, and outlook, which provide the incentive to crime. As a preliminary step I recently invited to a conference a number of academic authorities from several universities, in the various sciences touching on delinquency. As a result of their valuable help I am hopeful that new research projects may be started and that we may at last begin to tackle these most fundamental of all our problems." (*Penal Reform and Research*: Eleanor Rathbone Memorial Lecture by Mr. R. A. Butler, Liverpool University Press, 1960.)