in December, 1956, with the most highly attenuated currently available strains of each of the three types, have thus far produced no untoward reactions in vaccinees or their contacts. Spread of the vaccine viruses to others is an accepted fact in the immunization with live poliovirus vaccines, and this problem is not being "side-stepped" but is rather being carefully studied in various trials. The trials on some hundreds of thousands of children—some already completed, others now in progress, and still others to be initiated in 1959—carried out in accord with the stipulations of the Expert Committee on Poliomyelitis of the World Health Organization should provide us in the near future with the information necessary for a decision regarding the place of orally administered live poliovirus vaccines in the prevention and eradication of poliomyelitis.

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RESPONSE OF INFANTS TO A THIRD DOSE OF POLIOMYELITIS VACCINE GIVEN 10 TO 12 MONTHS AFTER PRIMARY IMMUNIZATION

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In our first study (Perkins, Yetts, and Gaisford, 1958) we reported that when infants aged 10 weeks or less were given a primary course of two doses of poliomyelitis vaccine the antibody response was in most cases unsatisfactory. This was due principally to the inhibiting effect of maternally transmitted antibodies, but also to the fact that a stronger antigenic stimulus is necessary in the newborn period to produce results comparable with those obtained in later infancy.

Despite the unsatisfactory results it was thought possible that, in at least some of the infants, primary immunization might have occurred but that we had been unable to demonstrate this because the increase in antibody level had been masked by the maternally transmitted antibodies. It was therefore decided to recall the infants approximately a year later and, from a study of the response to a reinforcing dose, obtain further information on the extent of any basal immunity which had been induced.

Procedures

Immunization.—Of the 88 infants previously studied, 80 were available. They were given 1 ml. of vaccine intramuscularly 10 to 12 months after their second dose. The vaccine used was Glaxo batch 13, which had been shown to have satisfactory antigenic activity by the routine test in monkeys (Biological Standards Control Laboratory, 1957). The infants, who were 1, 6, and 10 weeks old respectively at the time of injection of the first dose of vaccine, were designated as groups A, B, and C. In the present investigation there were 29 in group A, 28 in group B, and 23 in group C.

Titration of Sera.—The sera were titrated for poliomyelitis-neutralizing antibodies to each of the three virus types by the method previously described (Biological Standards Control Laboratory, 1957), which has been shown to give reproducible results (Perkins, Sousa, and Tobin, 1958). Fourfold serial dilutions of sera were used, the test dose of virus was approximately 100 $TCID_{50}$, and each serum-dilution/virus mixture was inoculated into two monkey-kidney-cell culture tubes. The two samples of serum from each infant were titrated in parallel in the same test, together with a repeat titration of the serum sample taken 14 to 21 days after the second dose. In the case of one infant in group B it was not possible to determine antibody levels to types 2 and 3 virus. All titres are given as the dilution of serum in the serum–virus mixtures before addition to cell cultures

Level of Antibody 10 to 12 Months After Two Doses of Vaccine

Almost all the infants who had not given a serological response to two doses of vaccine had either undetectable or very low antibody levels 10 to 12 months later. This was the case for all three virus types and for each age group. However, in most of those infants who had responded to primary immunization the titres had not fallen comparably, the antibody produced in response to active immunization having clearly been lost at a slower rate than the maternally transmitted antibody.

In 17 of the infants the antibody levels at the time of giving the booster dose were higher than those present immediately after the second dose—seven were in group A, five in group B, and five in group C. Of these 17 infants, eight had increased antibody levels to two types of virus and nine to one type. In all, there were eight with increased levels to type 1, nine to type 2, and eight to type 3. The increases were evenly distributed between infants who had responded to primary immunization and those who had not. In all cases the response to the booster dose was very high to the type in which the increase had occurred and much higher than the response of the remainder of the infants. These findings made it likely that intercurrent non-paralytic infection had occurred in these 17 infants, and they were therefore excluded from the analysis of the results. The infants remaining in the final analysis were 22 in group A, 23 in group B, and 18 in group C.

Response to a Booster Dose of Vaccine

The responses to the three virus types after receiving the booster dose are shown in Figs. 1, 2, and 3. The antibody titres of those infants who had responded to primary immunization—"primary responders"—are shown as open circles, and the titres of those who had not are indicated by black circles. The response to type 1 (Fig. 1) by the 22 infants in group A was very poor. None of these infants were primary responders and only five gave a small increase in antibody titre after the booster dose, the highest being 32. The results in groups B and C were better, 17 responding in group B and 16 in group C. The level in many, however, was not as high as would be expected if the infants had been sensitized by primary immunization.

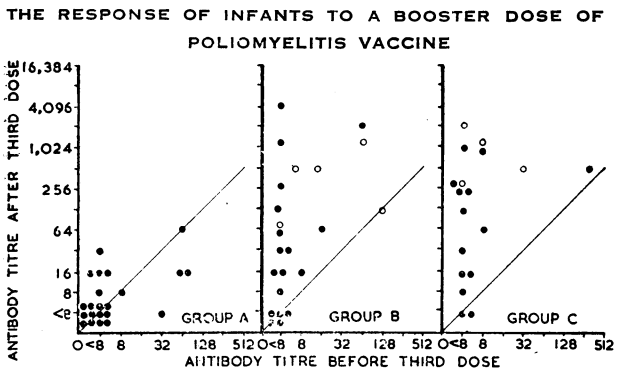

FIG. 1.—Serological response of 1-, 6,- and 10-weeks-old infants to type 1 virus. O=Infants previously responding to primary immunization. ●=Infants previously *not* responding to primary immunization.

Of the 32 infants in these two groups who were not primary responders, 20 had antibody levels of 64 or less, which were poor in comparison with the primary responders, all of whom had titres of 64 or more after the booster dose. Of the nine primary responders, eight showed increases in titre after the booster dose, the smallest increase being from <8 to 64 and the highest from <8 to 2,048. The remaining primary responder, who showed no increase, had a titre of 128 both before and after the booster dose. It is thus evident that the primary responders produced better levels after the booster dose than the majority of those who had not responded to primary immunization. Nevertheless, in groups B and C there were infants who had shown no apparent primary response but whose titres after the booster dose were as high as some of the primary responders. In all these subjects, however, the maternal antibody levels at the time of primary immunization were 256 or less.

The responses to type 2 (Fig. 2) show also that the older infants reacted better than the younger ones. Of the 62 infants in all, only seven failed to respond, five of whom were in group A and two in group B. In group A, all six primary responders gave higher antibody levels than all but 2 of the remaining 16 in the group, 5 of whom gave antibody levels of less than 64. In group B, 7 of the 10 primary responders gave antibody levels higher than all but 3 of the remaining 12 in the group. In group C, however, the seven infants who gave no apparent primary response gave as high antibody levels to the booster dose as the 11 primary responders.

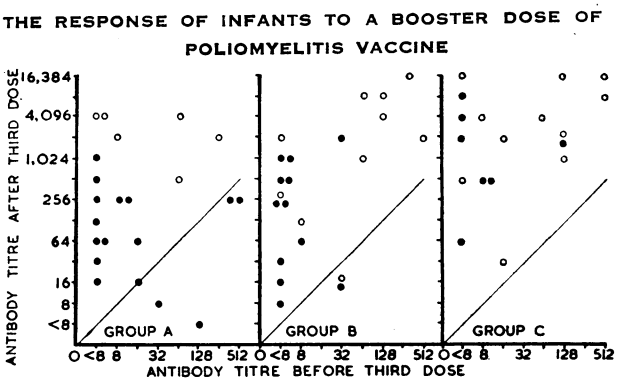

FIG. 2.—Serological response of 1-, 6-, and 10-weeks-old infants to type 2 virus.

The responses to type 3 (Fig. 3) were similar to those obtained to type 2. The three primary responders in

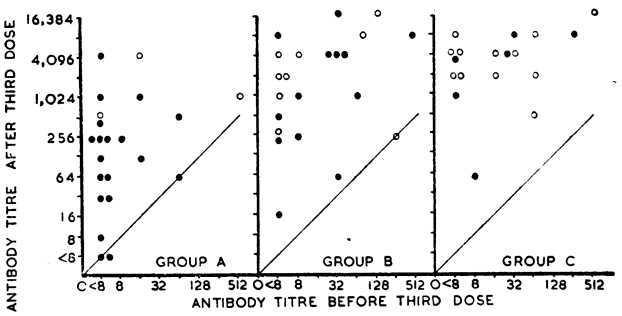

FIG. 3.—Serological response of 1-, 6-, and 10-weeks-old infants to type 3 virus.

group A gave higher antibody levels than 14 of the remaining 19 in the group, 3 of whom gave no response. In group B the primary responders gave antibody levels higher than some of the non-responders, whereas in group C this was not the case because the response to the booster dose was similar in both the primary responders and non-responders.

Discussion

These results of the responses of infants to a booster dose of vaccine give a clearer picture of the influence of maternally transmitted antibodies on primary immunization. High levels of such antibody completely inhibit active immunization against the homologous type. No infant with an antibody level of 1,024 or more before primary immunization gave a secondary response to the booster dose, indicating that primary immunization had been ineffective. This was true for all three virus types, although a high level of maternal antibody to one type had no inhibiting effect on the response to either of the heterologous types. Infants who had apparently not given a primary response, but whose secondary response was as good as that of the primary responders, had maternally transmitted antibody levels between 32 and 1,024; clearly these levels had not completely inhibited, but had merely masked, the primary response. Infants with low maternal antibody levels who had responded to primary immunization showed a good response to the booster dose. There were, however, a number who, in spite of the fact that they had low levels of transmitted antibody, did not respond initially — the "poor responders"—and these gave a similarly poor response to the booster dose.

It is also evident from the results that the best response is given by the 10-weeks-old infants, but these can by no means be regarded as satisfactory, and compare unfavourably, especially for type 1, with those obtained in 1- to 9-year-old children (Medical Research Council, 1957a, 1957b).

These results substantiate our initial conclusions that immunization in the first few weeks of life is unsatisfactory, especially to the type 1 virus. In order to be effective, primary immunization should produce substantial antibody responses to all three types in order to ensure an adequate secondary response to the booster dose. This is not likely to be achieved with existing vaccines unless immunization is delayed until the maternal antibody has fallen to a low non-inhibitory level, which may not be until the infants are 6 to 9 months old. These age groups are at present being studied.

Summary

A study was made of the effect of a third dose of poliomyelitis vaccine in a group of 80 infants who at the time of primary immunization were 10 weeks of age or less. The booster dose was given 10 to 12 months after primary immunization.

In 17 infants a rise in antibody titre occurred between primary immunization and the booster dose, indicating intercurrent poliomyelitis infection. These infants were excluded in assessing the effect of the booster dose.

Infants who showed an increase in antibody level after primary immunization also responded to the booster dose, but they all had low levels of maternally transmitted antibody. Those with high antibody levels at birth who gave no primary response did not react to the booster dose. A number with intermediate levels of maternal antibody who showed no apparent primary response reacted to the booster dose; in these, primary immunization had evidently occurred, but the rise in titre was masked by the maternal antibody.

In general, the infants who had started their primary immunization at 10 weeks of age responded better to the booster dose than those starting at 1 and 6 weeks old.

This study confirms our original conclusion that immunization of infants against poliomyelitis in the first few weeks of life cannot be regarded as satisfactory, especially with regard to the response to type 1 virus. It is possible that the earliest age when satisfactory mass immunization may be achieved is when the infant is 6 to 9 months old. This age group is at present being studied.

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SIDE-EFFECTS FOLLOWING TRIAMCINOLONE

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The initial reports on the use of triamcinolone (16α-hydroxy, 9α-fluorohydrocortisone) as a suppressive agent in rheumatoid arthritis were extremely encouraging. Originally announced by Hellman *et al.* (1957) at the American Rheumatism Association meeting at Bethesda in 1956, it was stated to possess powerful antirheumatic properties. They claimed that an average dose of 13.5 mg. daily resulted in a response superior to that observed with other steroids; metabolic balance studies suggested that little or no sodium retention or potassium or nitrogen loss occurred, and at that time no undesirable side-effects had been noted. Bunim (1957) agreed with these findings, but warned that it was much too early to draw any conclusions, as at that time only a few patients had been treated for short periods.

Later reports suggest that the side-effects normally associated with steroid therapy do in fact follow the prolonged administration of triamcinolone. Hollander