can be felt if the blood pressure is sustained for longer than four hours. Only one death in this series followed a prolonged pressor response.

Intermittent injection of metaraminol has proved successful in maintaining the blood pressure for several days if necessary. Unnecessarily frequent injections of small doses were used initially in order to avoid the hazard of a severe pressor response. With more experience, fewer doses of larger amounts have been used. The frequency of injection has been determined by repeated blood-pressure estimations at 10- or 15-minute intervals, metaraminol being given whenever the systolic pressure fell to 85 mm. Hg or less.

No tachyphylaxis has occurred with this drug as was met with in two patients receiving mephentermine.

In a further two cases metaraminol proved effective when mephentermine had failed to raise the pressure. This study was not intended as a comparison of the pressor effects of these two drugs, but solely to assess the value of metaraminol. No doubt the use of increasingly large doses of mephentermine would have achieved a pressor response in these patients. However, the repeated efficiency of identical doses of metaraminol has proved of great value.

It would appear that metaraminol is the drug of choice for intermittent parenteral use in cardiac shock and should therefore be of particular benefit in the domiciliary treatment of this condition.

Coincident heart failure or arrhythmias should be treated immediately: four of the survivors had suffered from one or more of these additional complications.

No undesirable side-effects have accompanied the use of metaraminol.

Summary

Results are presented of the use of metaraminol in 12 patients suffering from cardiac shock. This drug has a similar action to that of noradrenaline but has the advantage that it may be given by subcutaneous, intramuscular, or intravenous injection. For this reason it should prove of value in the domiciliary treatment of cardiac shock.

The 50% mortality in this series included all the patients with shock of four or more hours' duration. This observation is in accord with the experience of others, and demonstrates the need for early treatment of this complication of cardiac infarction.

The patients treated in this study were under the care of Drs. D. Evan Bedford and Walter Somerville. I am most grateful for the opportunity to undertake this work, and also for their encouragement and helpful criticism. I am grateful to the successive house-physicians who have assisted me so patiently. The metaraminol was kindly supplied by Merck Sharp and Dohme Ltd.

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A COMPARISON OF THE RESPONSES OF 100 INFANTS TO PRIMARY POLIOMYELITIS IMMUNIZATION WITH TWO AND WITH THREE DOSES OF VACCINE

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In previous investigations (Perkins, Yetts, and Gaisford, 1958, 1959) it was shown that in only a small proportion of infants under the age of 10 weeks could a satisfactory basal immunity be established by the injection of two doses of poliomyelitis vaccine. This was evident not only from the responses to primary immunization but also from those obtained when a booster dose was given 10 to 12 months later. It was concluded that two factors were responsible for the poor responses—namely, the inhibiting effect of maternally transmitted antibody and the necessity for highly potent antigens in early infancy. In view of these findings, two further studies were made. The first, with 1-week-old infants, was designed to determine whether the inhibiting action of maternal antibody could be overcome by increasing the number and size of the doses. The second study, with 16-weeks-old infants, was made in order to determine whether infants of this age had reached a stage at which their immunological activity would overcome the inhibiting effect of passively acquired antibodies and also to investigate whether a more substantial basal immunity could be established by three doses than by two. By analogy with pertussis and diphtheria immunization in infants it might be expected that poliomyelitis would require a similar course, and that, if the vaccine was comparable in antigenicity to pertussis vaccine and diphtheria toxoid, results might be similar.

Procedures

One-week-old Infants.—In this group there were 45 infants, of whom 36 received three doses and 9 received only two. The vaccine was given at intervals of four weeks, and all infants were 1 week old at the time they received the first injection. Each dose was 2 ml., which was double the normal, and was given by injecting 1 ml.

into each buttock. The total volume was thus 4 ml. for those who received two doses and 6 ml. for those who received three. Serum was collected from the cord blood of all infants and served as the pre-immunization sample. Post-immunization serum samples were taken (1) four weeks after the second dose, which was at the time of the third dose, and (2) 14 to 21 days later. Samples were obtained after both the second and third doses from 27 infants, after the second dose only from 9, and after the third dose only from the remaining 9.

Sixteen-weeks-old Infants.—55 infants were given three doses of vaccine intramuscularly, each of 1 ml., spaced at intervals of four weeks.. All were 15 to 17 weeks of age at the time they received the first dose. From all infants serum samples were collected from the cord blood, and pre-immunization samples were taken on the day the first dose of vaccine was given. Post-immunization samples were taken from 43 after both the second and third doses, from 6 after the second dose, and from the remaining 6 after the third dose only. As with the 1-week-old infants, samples were taken four weeks after the second dose and 14 to 21 days after the third.

Vaccine.—Two vaccines were used in each group. One of these, Glaxo batch 24, was prepared from Brunenders (type 1), MEF-1 (type 2), and Saukett (type 3) strains, whilst the other, Connaught batch 75, differed from the British vaccine in the type 1 component, for which the Mahoney strain was used. The two batches, which showed similar antigenic activity in monkeys, were distributed equally between the two age groups, and, because the responses to both vaccines were similar, the results from each group have been combined.

Titration of Sera.—Sera were titrated by the method used in the previous investigations. For each infant all serum samples were titrated in parallel in the same test in order that a valid comparison of antibody levels could be made. All titres are given as the dilution of serum in the serum–virus mixtures before the addition to cell cultures.

Antibody Levels in Cord Blood and Loss of Maternally Transmitted Antibody in Infants

Table I gives the distribution of antibodies in the cord sera of 100 of the infants. The group was very similar to the one in the previous study (Perkins *et al.*, 1958) in that a large proportion (59) had antibodies to all three types and only five had no antibodies to any of the types. There was considerable variation in the antibody levels, which ranged from 8 to 16,384 for each type. The number of infants with no detectable antibody to one particular type was similar, being 23 for type 1, 17 for type 2, and 24 for type 3.

TABLE I.—*Distribution of Poliomyelitis Antibodies in the Cord Sera of 100 Infants*

No. of Sera	No. of Sera with Antibodies to:			
	No Type	One Type Only	Two Types Only	Three Types
100	5	16	20	59

The loss of maternal antibody in the 16-weeks-old infants is shown in Table II, in which the mean titre of the sera obtained at the time of giving the first dose of vaccine is compared with that of the cord sera. The loss of maternal antibodies was similar for each type, and such a decline is consistent with the findings of our earlier report that the maternal antibody level was halved every 21 days.

TABLE II.—*Loss of Maternal Antibody in 16-Weeks-Old Infants*

No. of Sera	Virus Type	Geometric Mean Antibody Titre of Sera of		Loss of Antibody
		Cord	Infant	
38	1	485	20	96%
41	2	625	24	96%
38	3	135	7	95%

Response of 1-week-old Infants to Two and Three Doses of Vaccine

The antibody responses of the 1-week-old infants to two and three doses of vaccine each consisting of 2 ml. is shown in Fig. 1 for the three virus types; the responses to two doses are shown as black circles and those to three doses are shown as open circles.

In general the results were disappointing for all three types. In the case of those infants with no maternal antibody the responses to three doses (6 ml.) were very much better than those to two doses (4 ml.). After two doses, only 1 of 9 responded to type 1, 4 of 8 to type 2, and 6 of 9 to type 3, whereas after three doses the

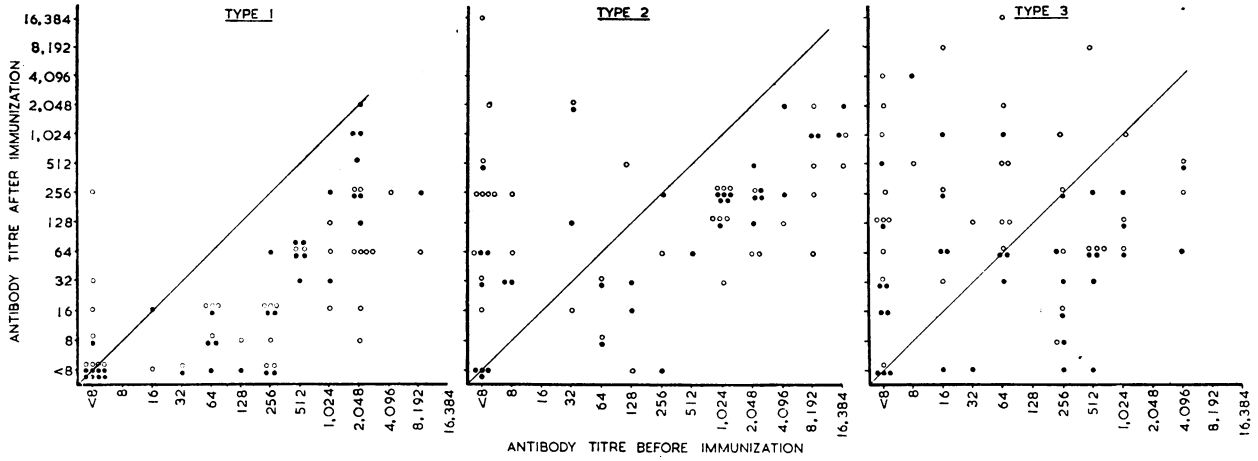

FIG. 1.—The response of 1-week-old infants to two and three doses of poliomyelitis vaccine. ●=Response after two doses O=Response after three doses.

corresponding figures were 4 of 8, 10 of 10, and 9 of 10. The higher activity of the three-dose schedule was also evident from the increase in antibody levels, especially for types 2 and 3, the mean titres after two doses being 1, 6, and 14 and after three doses 6, 274, and 157 for types 1, 2, and 3 respectively.

In the case of those infants with maternal antibody, it is seen from the figures that with each type a high proportion showed no apparent responses. It is also seen that there were no striking differences between the responses to two and three doses. With type 1, no responses were observed after either two or three doses; with type 2 there were four after two doses and four also after three doses; with type 3, six responded after two doses and 13 after three.

It is interesting to note that for those infants with high maternal antibody levels to types 1 and 2—namely, those with a titre of 2,048 or more—the responses after three doses were in almost all cases lower than those after two. This was no doubt due to the fall off in maternal antibody levels during the period between the second and third doses. For those infants with intermediate maternal antibody levels—titres from 16 to 1,024—the third dose appeared to have had little effect with types 1 and 2, but with type 3 many of the infants gave an increase in antibody levels.

Response of 16-weeks-old Infants to Two and Three Doses of Vaccine

The antibody responses of the 16-weeks-old infants are shown in Figs. 2 and 3. It is seen that those infants with no maternal antibody (Fig. 2) responded better to three doses of vaccine than to two. This was shown both by the proportion of infants responding and by the values of the geometric mean titres. For type 1, 7 of 22 responded to two doses, with a mean titre of 3, and 20 of 24 to three doses, with a mean titre of 23. For type 2, all the infants responded to both two and three doses, but the mean titre of 83 obtained after two was substantially less than that of 477 after three doses.

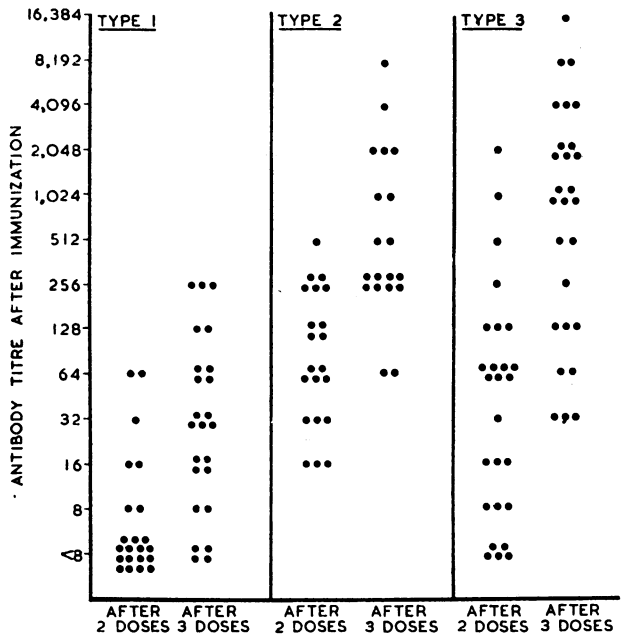

FIG. 2.—The response of 16-weeks-old infants with no maternal antibody to two and three doses of poliomyelitis vaccine.

For type 3, 21 of 26 responded to two doses with a mean titre of 30 and all responded to three doses with a mean titre of 695.

The results obtained in those infants with maternal antibody before immunization also showed that three doses of vaccine gave better responses than two. For type 1, only 3 of 27 infants had increased antibody levels after two doses compared with 9 of 25 after three doses; for type 2, 11 of 28 responded to two doses compared with 18 of 29 to three doses; and for type 3, 12 of 23 infants responded to two doses and 20 of 22 to three.

It is to be noted that the responses to types 1 and 2 with three doses of vaccine show evidence of maternal antibody interference. With type 1, 6 of the 11 infants with maternal antibody levels of 32 or less had titres greater than any of the 14 infants in whom the maternal antibody level was 64 or more. With type 2, 12 of 13 infants with maternal antibody levels of 32 or less responded, compared with 6 of 16 infants with maternal antibody levels of 64 or more. With type 3, however, there was less evidence of maternal antibody interference, but this was undoubtedly due to the lower levels of maternal antibody to this type and possibly to the greater antigenicity of this component of the vaccine.

Discussion

The incidence of maternally transmitted antibodies in the infants in this study was very similar to that of the infants previously recorded, and the loss of maternal antibody during the first 16 weeks of life was consistent with the previous findings that the level was halved approximately every 21 days.

It is evident from the results with the 1-week-old infants that the responses to two doses, each of 2 ml., were no better than those obtained previously in a similar group given two doses, each of 1 ml. On the other hand, three doses, each of 2 ml., produced a better response, but even with this schedule there was a high proportion of non-responders to all three types, particularly to type 1 and also among those infants possessing maternal antibody. In general, the responses to the three-dose schedule were no better than those obtained in the previous investigation in which 6-weeks-old infants were given two doses, each of 1 ml. It is thus difficult to know whether the increased responses to three doses were a result of the greater antigenic stimulus or of the increased age of the infants and hence their lower maternal antibody levels at the time of the third dose. It is probable that both factors play a part, but nevertheless it is quite clear that immunization at the age of 1 week, either with a two- or three-dose schedule or with a larger volume of vaccine, does not produce satisfactory results.

With the 16-weeks-old infants more encouraging results were obtained. With those who had little or no maternal antibody the responses to two doses, each of 1 ml., were no better than had been obtained in the previous study with 10-weeks-old infants on a similar schedule. On the other hand, three doses gave a decided improvement, 83% of the infants responding to type 1 and all to types 2 and 3; the geometric mean antibody titres reflected the greater immunizing power of the three-dose schedule.

Although a high proportion of infants with no maternal antibody responded to immunization, less

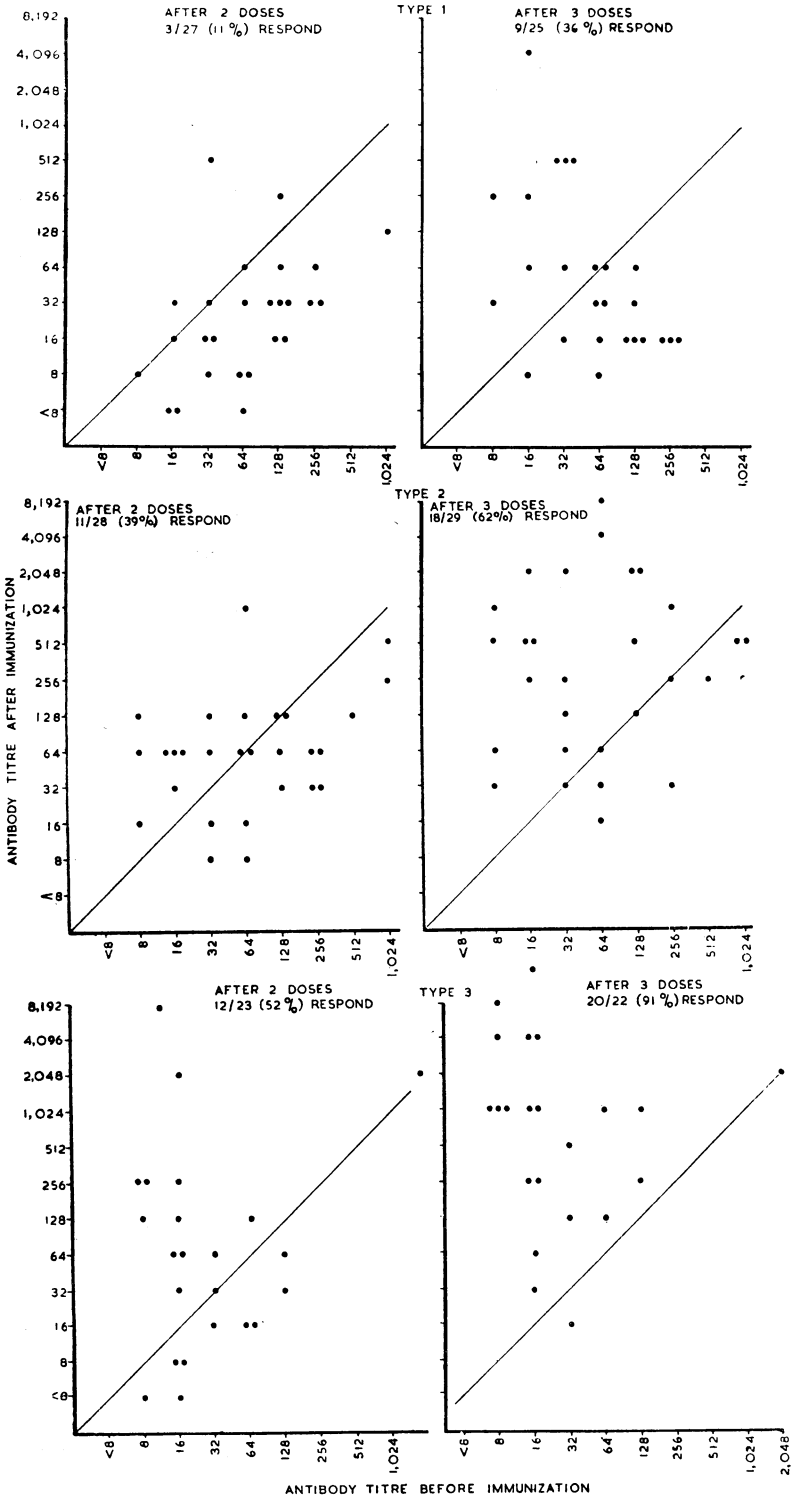

FIG. 3.—The response of 16-weeks-old infants with maternal antibody to two and three doses of poliomyelitis vaccine.

satisfactory results were obtained with those who had maternal antibody. After two doses, only 11% responded to type 1, 39% to type 2, and 52% to type 3, and after three doses the corresponding figures were 36%, 62%, and 91%. It is thus evident that the three-dose schedule was unable in all cases to overcome the maternal antibody interference, especially with type 1. It is probable, however, that these figures do not give an entirely true picture of the actual number responding to primary immunization, since in some cases the response may not be apparent because of masking by maternal antibody; the true picture will be revealed when a booster dose is given in a year's time. Nevertheless, the present results provide ample evidence to indicate that maternal antibody interference is occurring.

It is clear that, of all the groups so far studied, the 16-weeks-old infant, when given three doses of vaccine, responded best. This response, however, cannot be considered satisfactory, because immunization has not been achieved in all infants, especially in the case of type 1—the most important component of the vaccine. It would therefore seem advisable—as we have said previously—to delay immunization against poliomyelitis until maternal antibody has reached a non-inhibitory level.

Summary

The response of infants to poliomyelitis vaccine is governed by two factors—the level of maternal antibody and the number of antigenic stimuli given in the course of primary immunization. Two groups of infants, 45 aged 1 week and 55 aged 16 weeks, were studied. The 1-week-old infants had such high levels of maternal antibody that doubling the volume and giving three doses of vaccine resulted in no better response than that given by the normal immunization schedule in similar infants in the previous study. Satisfactory responses were obtained with the ordinary dose of 1 ml. in the 16-weeks-old infants who had very low maternal antibody levels, especially after the third dose of vaccine. In this age group, however, inhibitory levels of maternal antibody were present in some infants, and in order to obtain satisfactory immunization to all types in all infants it is suggested that immunization should be delayed until 6 to 9 months of age, at which time three doses of vaccine should be considered as a course of primary immunization.

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