With any preparation of multiple antigens, a basic question is the possibility of immunologic interference or enhancement. This paper reports a study on 48 infants from two to four months of age who received a multiple vaccine against diphtheria, tetanus, pertussis, and poliomyelitis. Maternal antibodies, when present, appeared to suppress both the primary and booster response to the several antigenic components.

SEROLOGIC RESPONSE OF INFANTS TO A MULTIPLE VACCINE FOR SIMULTANEOUS IMMUNIZATION AGAINST DIPHTHERIA, PERTUSSIS, TETANUS, AND POLIOMYELITIS, IN RELATION TO THE PRESENCE OF SPECIFIC MATERNAL ANTIBODY

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THERE ARE obvious advantages in the use of a preparation of multiple antigens for simultaneous immunization against several diseases. Decreasing the number of injections, for example, becomes an important objective with the ever-increasing number of specific antigens available for active immunization; it is important, too, in relation to the current emphasis on early immunization of infants. A growing number of combined prophylactics have been suggested, and some have been subjected to field study. Triple vaccine containing diphtheria and tetanus toxoids and pertussis vaccine (DPT) has been in common use in the United States for a number of years; and recently, studies have been directed towards the inclusion of poliomyelitis antigens to make a quadruple vaccine (DPT-polio) for simultaneous immunization against all four diseases.

While the triple antigen has been used on a large scale with apparent success, the inclusion of poliomyelitis vaccine (Types I, II, and III) with the other three antigens, introduces new factors in the manufacture of the resulting multiple vaccine, and it must be evaluated as a new product. A basic question which needs examination, as with any preparation of multiple antigens, concerns the possibility of immunologic interference or enhancement. That is, does any one of the several antigens interfere with the immunologic response to any of the others, or, is the

response of any one enhanced by combination with the others? The question also arises whether the presence of specific antibody—actively produced, or passively acquired by the infant as maternal antibody—either increases or suppresses the immunologic response. In experiments in animals, using a combination of DPT and polio vaccine, Kendrick and Brown[1] observed that there was a serologic response to each component; in monkeys, there was some indication of enhancement of the response to poliomyelitis antigens in the combined product in comparison with poliomyelitis vaccine given alone. Schuchardt, Munoz, and Verwey[2] compared triple with quadruple vaccine in potency tests in animals and observed that with the two products the results were similar for diphtheria and tetanus toxoids and for the pertussis component; in monkeys, the potency of the poliomyelitis component was greater with the quadruple than with poliomyelitis vaccine alone except in the instance of Type I which they pointed out was a weak antigen.

For immunization of children, Batson, et al.,[3] mixed poliomyelitis vaccine with pertussis vaccine and also with triple vaccine in the syringe used for injection and observed no interference among the several antigenic components; neither did they observe any influence of maternal antibodies on the response. Barrett and co-workers[4,5] injected children from two and a half months to five years of age with the product Quadrigen* in which the four antigenic components were combined during manufacture. These authors found that the antibody levels following the primary immunization series were not as high in infants of less than six months as in older children. They stated that the presence of maternal antibody made the results more difficult to evaluate and concluded that the response to a booster injection is a more meaningful criterion for evaluating the effectiveness of vaccine than the primary response.

The official release of multiple antigen preparations containing diptheria and tetanus toxoids and pertussis and poliomyelitis vaccines for use in the United States and in Canada, and the recommendation of such preparations by the Multiple Antigens Committee of the American Public Health Association,[6] emphasize the importance of the accumulation of as much basic information as possible on the use of these products. In this paper, the data are concerned particularly with the effect of passively acquired maternal antibody on the infant's response to the several component antigens.

Plan of Study

The clinical portion of this study was undertaken by Drs. Watson and Giammona, Department of Pediatrics, University of Michigan Medical School, who are reporting these aspects elsewhere.[7]

Forty-eight healthy infants who were registered at the Well Baby Clinic of the University of Michigan Hospital were from two to four months of age at the time of their first injection with 0.5 ml of a multiple vaccine† containing diphtheria, tetanus, pertussis, and trivalent poliomyelitis antigens (DPT-polio). Second and third injections of 0.5 ml each were given at intervals of one month. Thirty-one of the children received a fourth or booster dose of the same material, most of them from six to eight months later, a few after a year. Blood specimens were obtained from all 48 children at the start of the study and again two weeks after the

* Trade name, Parke, Davis & Company.

† The vaccine (Quadrigen) was kindly supplied by its manufacturers, Parke, Davis and Company, who also supported financially the clinical portion of the study.

primary series of injections. Prebooster specimens were obtained from only five of those receiving the additional injection but all 31 were bled from three to four weeks following it. The sera were maintained at 4°C until tested.

Laboratory Methods and Results

Diphtheria and Tetanus

The diphtheria and tetanus antitoxin levels were determined in the laboratories of Parke, Davis and Company, Detroit. Serum specimens for these tests were available on 42 of the 48 infants. The antitoxin levels have been grouped in terms of units as shown in Table 1. It will be seen that 31 of the 42 infants tested for diphtheria antitoxin had prevaccination levels of less than to the diphtheria, tetanus, and munization, 28 of these showed an increase to levels of between 0.1 and one unit and two had increased to more than one but less than 10 units. Of the 11 infants with preimmunization levels between 0.1 and one unit only two showed an increase following the primary series.

Thirty-seven of the 42 infants tested for tetanus antitoxin had preimmunization levels of less than 0.1 unit. All showed an increased level and most of them had more than one unit following vaccination. Of the five infants with detectable levels prior to immunization, two showed an increase.

Postbooster diphtheria and tetanus antitoxin levels were available for only 19 of the 42 infants. Thirteen and 17 of these, respectively, had less than 0.1 unit of diphtheria and tetanus antitoxin prior to primary vaccination; and after the booster injection, all showed a further increase over the postprimary level. Only 6 of the 19 infants had detectable diphtheria antitoxin before primary vaccination; following booster, three remained at the same level, and three increased. The two infants with detectable tetanus antitoxin before vaccine showed increased levels following booster.

Pertussis

Pre- and postprimary vaccination specimens from 47 of the 48 infants were tested for serologic response to the pertussis component of the quadruple vaccine, in terms of specific agglutination, using a rapid, reduced volume procedure.[8] Briefly, 0.1 ml of each serum dilution was mixed with 0.1 ml of a killed suspension of B. pertussis of 20 opacity units by NIH standard, the mixtures were shaken for three minutes, salt solution added, the tests read, and the results expressed in reciprocal titers of the highest final serum dilution at

Table 1—Diphtheria and Tetanus Antitoxin Levels in the Sera of 42 Infants Before and Following Vaccination with DPT-Polio

	Number of Infants at Each Level of Antitoxin					
	Prevaccination		Postvaccination			
	Units	Numbers	<0.1	0.1 to 1.0	1 to 10	>10
Diphtheria	<0.1	31	1	28	2	
	0.1 to 1.0	11	2	7	2	
Tetanus	<0.1	37		2	28	7
	0.1 to 1.0	3		2	1	
	>1 to 10	2	1			1

Table 2—Pertussis Agglutinin Titers in 47 Infants Before and Following Vaccination with DPT-Polio

Prevaccination		Postvaccination Titers			
		Number of Infants in Each Range			Geometric
Titers	Number	Negative	4-16	32-128	Mean
Negative	43	14	13	16	10.35
16	1	1	0	0	Negative
32	3	1	2	0	4.00

which definite agglutination was observed.*

In Table 2, the results with postvaccination sera have been arranged according to the titers of samples taken before vaccination. Of 43 infants without demonstrable prevaccination antibodies, 14 (approximately one-third) remained negative—a lower response than would be expected following a strongly antigenic vaccine. There were only 4 of the 47 infants who had positive agglutination tests before vaccination, that is, who had measurable maternal antibody in their serum; and all four had lower titers after primary vaccination than before. This suggests that there had been progressive elimination of maternal antibody without active serologic response of the infant. The question immediately arises as to whether the apparent depressive effect of circulating maternal antibody on postprimary response would still be observed after a later booster injection. In Table 3, the postprimary and postbooster results in 30 infants suggest that the increased titer expected in a secondary response was obtained only in those infants without detectable agglutination before vaccination. In the four infants with measurable prevaccination antibodies the postprimary titers showed a decrease; and the response was still depressed after the booster injection six months later. The preprimary, postprimary, and post booster titers of these four infants were, respectively: 32, 8, 4; 16, 4, 8; 32, 4, 4; 32, 4, 4. The numbers are small and do not warrant firm conclusions, but the results are consistent with the hypothesis that the presence of maternal antibody depressed the serologic response of the infant to primary vaccination, and also that this depressive effect may still be present after a booster injection six months later. The effect of a still later booster injection under these conditions was not studied.

Poliomyelitis

Poliomyelitis antibody levels were determined by performing neutralization tests against standard strains of the three types of virus in plastic panel tissue cultures of monkey kidney cells.[10] Pre- and postvaccination sera were availfor all 48 infants and were always tested together on the same day. Antibody titers are expressed in terms of the reciprocal of the highest original serum dilution which neutralized 100 tissue culture doses of virus. Since most of the mothers had received poliomyelitis vaccine during pregnancy or within the two years preceding, many of their infants had detectable antibodies at the

* As explained elsewhere,[9] if these titers are to be compared with those obtained in the one-ml volume tests, the titers obtained in the rapid test should be multiplied by five, in order to assure comparison of reactions between equivalent amounts of serum and antigen.

time they received the first injection. As indicated in Table 4, only 18 had no detectable antibodies to Type I virus at the lowest dilution tested (1:4), ten were negative for Type II, and 22 for Type III. Only four were "triple negative." The geometric mean antibody titers of the prevaccination specimens were 7, 19, and 7 for Types I, II, and III, respectively. The postprimary vaccine mean titers for the same three types were 7, 24, and 22, indicating that except for Type III very little antibody development had been induced by the vaccine. However, examination of the postprimary vaccination titers in relation to their corresponding prevaccination titers reveals a startling fact. Of the 18 negative for Type I before vaccination, seven developed antibodies, as did nine of ten negative for Type II, and 18 of 22 for Type III. In contrast, only 5 of the 30 with prevaccination antibodies to Type I, 8 of 38 for Type II, and 7 of 26 for Type III showed a rise in antibody titer after primary vaccination! Furthermore, most of the infants with prevaccine antibodies that showed a subsequent rise in titer had very low titers (either four or eight) before immunization. When the prevaccine titers were 16 or greater, the titers of the vast majority of them decreased following the three injections, many to such an extent that antibodies were no longer detectable. In some children the titers of antibody to the three types varied independently of each other; the titer of antibodies for two types might decrease while the titers of a third would develop following vaccine, particularly if not present in the prevaccine specimen. Two examples of this phenomenon are shown:

	R.H.		
	I	II	III
Prevaccine	16	<4	64
Postprimary	<4	8	<4
Postbooster	<4	256	<4

	S.K.		
	I	II	III
Prevaccine	<4	256	<4
Postprimary	256	256	1024
Postbooster	256	8	1024

These results suggest strongly that passively transferred maternal antibodies, if present in titers of 1:16 or greater, interfere with the response to active immunization with poliomyelitis vaccine.

In Table 5, the results for the 31 infants who received booster injections from six months to one year following the third dose of the primary series were arranged according to those infants with maternal antibodies (by type) at the time of their first injection, and those without antibodies. The prevaccination geometric mean titers of those with maternal antibodies were 24, 35, and 22 for Types I, II, and III, respectively. The mean titers of these same indi-

Table 3—Pertussis Agglutinin Titers in the Sera of 30 Infants Before and Following Primary and Postbooster Vaccination with DPT-Polio

Prevaccination		Postprimary				Postbooster			
Titer	Number	Negative at 1:4	4-16	32-128	Geometric Mean	Negative at 1:4	4-16	32-128	Geometric mean
Negative	26	7	7	12	10.44	0	11	15	23.87
16	1	1	0	0	Negative	0	1	0	8.0
32	3	1	2	0	4.0	2	1	0	2.57
Total	30	9	9	12		2	13	15	

Table 4—Effect of Vaccination with DPT-Polio on Poliomyelitis Neutralizing Antibody Titers in the Sera of 48 Infants

Type	Prevaccination		Postvaccination		
	Titer	Number	Increase	Same	Decrease
I	<4	18	(7)	11	—
	4-8	9	(4)	1	4
	16-64	20	1	1	(18)
	>64	1	0	0	1
II	<4	10	(9)	1	—
	4-8	7	(6)	0	1
	16-64	22	2	4	(16)
	>64	9	0	1	(8)
III	<4	22	(18)	4	—
	4-8	12	(6)	0	6
	16-64	13	1	2	(10)
	>64	1	0	0	(1)
All types	Negative	50	(34)	16	—
	4-8	28	(16)	1	11
	16-64	55	4	7	(44)
	>64	11	0	1	(10)

NOTE: numbers in parentheses are for special emphasis.

viduals were only 4, 17, and 12 following the primary series and an additional booster injection six months later. In contrast, the postbooster means of those with no detectable antibody before vaccination were 27, 161, and 268 for the three types, respectively. It will be seen that of eight infants with no detectable antibodies to Type I virus before vaccination, five were still in the <4 category after the primary series; all but one, however, had developed antibodies as a result of the booster injection. In contrast, of 17 infants with prevaccination titers of 16 or 64, most were lower in titer following primary and 11 were <4 following the booster injection. This pattern of antibody titer shift is essentially the same for all three types. Thus it is clear that the presence of maternal antibodies inhibited not only the primary response, but, under the cover of maternal antibodies in high titer, vaccine did not condition the infants to the booster phenomenon. This is further illustrated in Table 6, which shows the results of all tests on the only five infants who were bled immediately prior to the booster injection.

Discussion

It was not the primary purpose of this study to measure the efficacy of the multiple vaccine or to investigate the antigenicity of its individual components in comparison with the same antigens given separately. By the strictest of the requirements for measurement of antigenicity of a vaccine, namely, the response of children with no detectable specific antibodies before vaccination, the components measured up well. In fact, the conversion of "negatives" to "positives," in terms of antibody was very good for the diphtheria and tetanus but was somewhat less than expected for the pertussis and poliomyelitis. Nor is it the purpose of the study

to interpret serological responses in terms of actual protection against given diseases. It is recognized that measurable antibodies, especially those determined by neutralization tests, provide an index of probable protection, but immunity can exist in the absence of detectable antibodies. Conversely, the presence of antibodies in high titer is no guarantee of absolute protection against invasion and infection with any of these agents.

Granted, then, that immunity is relative, the investigator should be concerned with any factor which interferes with the development of antibodies following experience with an antigen. One such factor appears to be evident in this study, namely, the suppressive effect of maternal antibodies on the antibody response of infants to vaccination. Although only a small number of infants had persisting maternally acquired antibodies to diphtheria, tetanus, and pertussis the data were sufficient to illustrate this phenomenon. The vaccine was successful in stimulating an increase in measurable antibody in only 2 of 11 such infants with diphtheria antibodies, two of five with tetanus, and none of four with pertussis agglutinins before vaccine. These results are entirely in keeping with the more extensive data observed in the study of poliomyelitis antibody response. Due to the recent vaccination of most of the mothers against this disease a very high proportion of the infants had high levels of maternal antibody at delivery. Thirty of 48 had demonstrable antibodies for Type I, 38 for Type II, and 26 for Type III. As mentioned previously only four infants failed to show antibodies for at least one type of virus. Only 16 per cent, 21 per cent, and 26 per cent of the infants with antibodies showed an increased titer to the three types, respectively, following vaccination. Perhaps more pertinent to the question of suppression is the fact that antibody titers actually decreased in the majority of such infants. This was true of pertussis as well as poliomyelitis and to a lesser extent of diphtheria and tetanus.

Suppression of active immunization by passive antibodies is not newly recognized. Talmage[11] states that transfer of serum from an immunized to a normal animal has been shown to suppress rather than accentuate the sub-

Table 5—Poliomyelitis Neutralizing Antibody Titers in the Sera of 31 Infants Before and Following Primary and Postbooster Vaccination

	Prevaccination		Postprimary							Postbooster						
Type	Titer	No.	<4	4	8	16	64	256	1,024	<4	4	8	16	64	256	1,024
I	<4	8	5		1		1	1		1	2	1		2	1	1
	4-8	5	2	1	1	1				2			1	2		
	16-64	17	6	2	4	5				11	2	3	1			
	>64	1					1			1						
II	<4	6	1		1	1	1	1	1					3	2	1
	4-8	6	1		1	1	2	1		1		1		1	3	
	16-64	14	3	2	4	4	1			3	1		4	4	2	
	>64	5		1			3			2	2	1				
III	<4	15	1		3	2	1	6	2	1				4	3	7
	4-8	6	2	1		1	2			1				3	2	
	16-64	9	4	1		3	1			6	1		1		1	
	>64	1					1				1					

Table 6—Individual Poliomyelitis Neutralizing Antibody Titers of Five Infants by Type

Serum Specimen	J.C.			R.N.			N.J.			J.R.			T.W.		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
Preprimary	64	8	16	4	64	<4	16	8	64	8	64	4	8	8	<4
Postprimary	<4	<4	<4	<4	16	<4	<4	16	4	<4	8	<4	16	64	16
Prebooster	<4	<16	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4	4	<4	<4
Postbooster	8	64	16	64	<4	64	<4	256	<4	16	16	64	64	8	64

sequent antibody response. di Sant' Agnese[12] found that newborn children did not respond as well as older children to diphtheria immunization but observed that this condition was corrected following a booster dose. However, he added that the final response was better when the booster was given a year later rather than after six months. Additional examples of this phenomenon are cited by Edsall[13] in a recent review. The inferior response of young infants to poliomyelitis vaccine has been observed recently by several authors.[4,5,14-19] Some of these authors associated this inhibition with the presence of maternally transferred passive antibodies.[15-20] Since there is ample evidence that older children and adults with actively produced antibodies respond well to vaccination, the obvious conclusion is that the difference which exists between the two types of response is not related to the presence or absence of antibodies per se, but to whether they were passively acquired or actively produced by the individual himself. In the latter case the antibody forming mechanism has been activated by either natural exposure or previous vaccination and additional stimuli are therefore capable of enhancing the output of antibodies.

In the case of passively acquired circulating antibodies, no host mechanism is operating and the combination of antibody with antigen may represent the phenomenon of the neutralization test in vivo. This theory is supported by the present data which show that interference with active immunization is more likely to occur in the presence of higher concentrations (titer of 1:16 or higher) of passively acquired antibodies. A previous study[21] has shown that children respond very well to poliomyelitis vaccine administered three days following gamma globulin in double the usual prophylactic dose. This amount of gamma globulin, however, was shown to be detectable only in very low titer (1:2 or 1:4) in the circulating blood and for a limited time not exceeding three weeks.[22] The titer of passive maternal antibodies acquired by the infant can be very high depending upon the level in its mother, and can persist for many months.[17] Thus the level of mother's antibodies appears to be the governing factor in the serologic response of her infant to vaccine.

In a study beginning in 1954, poliomyelitis vaccine was reported to be reasonably effective in stimulating antibodies in two- to four-month-old infants.[23] Very few of the babies had antibodies at this age since the practice of routine vaccination of pregnant women had not yet been inaugurated. During recent years, however, many more women have poliomyelitis antibodies at the same time of delivery. Since it has been shown that the poliomyelitis antibody titer of mother's blood and cord blood are very similar,[23,24,14] and of mother's blood, cord, and new-

born infant's blood,[17] and since persistence of these passive antibodies in babies is a function of the original titer,[23,17,14,25] it seems clear that interference with active immunization of the infant is becoming more rather than less of a problem. This is illustrated by the findings in a study undertaken in 1956 in which 30 per cent of unvaccinated and 71 per cent of vaccinated women had antibodies for all three types of poliomyelitis virus at the time of delivery.[17] In a survey made in 1958, 83 per cent of 100 pregnant women, most of them recently vaccinated, had antibodies to all three types of virus.[26]

This increasing incidence of maternal antibodies is reflected in the present study where over 90 per cent of the infants had antibodies for one or more types three months following birth. A similar study in Canada by Wilson, et al.,[19] reports that less than 50 per cent of their infants had maternal antibody to poliomyelitis before vaccination; however, over one-third of them were five months of age or older, which may explain the better serological response to multiple vaccine found in their study in comparison with the present data.

The concern for possible inhibition of poliomyelitis antibody production in infants does not apply equally to the response to the diphtheria, tetanus, and pertussis components, since few of the mothers had detectable antibodies to these diseases as reflected by the prevaccination testing of their infants in the present study. In the 1956 report mentioned above only 5 of 95 mothers had pertussis agglutinins at the time of delivery, and in the 1958 survey, 15 of 100 were positive.

In view of the data presented it would seem that there should be serious consideration of delaying poliomyelitis vaccination of infants until maternal antibodies are more likely to be gone or at least reduced to a low level. The child is less frequently exposed early in infancy, and furthermore he should be protected during this interim by the same passively acquired antibodies which suppress the response to vaccine. Such a delay in administration would not necessarily preclude the combination of poliomyelitis vaccine with "triple" vaccine since perhaps it, too, could be delayed without serious consequences.

Summary

Forty-eight infants from two to four months of age were injected three times at intervals of one month with 0.5 ml of a multiple vaccine against diphtheria, tetanus, pertussis, and poliomyelitis. Thirty-one of the children received an additional or booster dose from 6 to 12 months later.

Serologic tests on prevaccination blood specimens revealed that very few of the infants had detectable antibodies to diphtheria, tetanus, or pertussis, but the majority of them had poliomyelitis antibodies at this time.

The response of the majority of the infants to the poliomyelitis components of the vaccine was definitely poorer than to the diphtheria, tetanus, and pertussis components.

The lower serologic response to the poliomyelitis antigens was clearly associated with the presence of maternally acquired passive antibodies in the infant's serum at the time of vaccination. The few children who had prevaccination antibodies to diphtheria, tetanus, and pertussis also had poorer response than did those who were negative before vaccination.

The suppressive effect of maternal antibodies affected not only the primary, but also the booster response to the several antigenic components; tetanus antibody production seemed to be least influenced. The significance of the findings is discussed.

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