PERTUSSIS ANTIBODY RESPONSE AFTER TRIPLE ANTIGEN

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In the search for safe methods of immunization it must not be forgotten that the primary object of the procedure is to protect against a particular disease. As the minimizing of undesirable side-effects is obviously most important the safest antigens may be those in which potency has been reduced. For some time it has been found useful to add alum to pertussis and diphtheria antigens and this has increased their potency, but with improvements in preparation pertussis vaccine has been prepared in saline suspension and excellent results obtained. The addition of diphtheria toxoid to a pertussis antigen has been found to potentiate the antigenic power of the diphtheria toxoid (Ungar, 1952).

With the introduction of triple antigens the problem of antagonism was raised (Barr and Llewellyn-Jones, 1953), and care was needed to arrange the various constituents in such proportion that a response was obtained to all three antigens sufficient to produce immunity to each. Such preparations are in existence and have been used satisfactorily, but most have contained a mineral carrier.

Because of the fear of local complications and, more especially, on account of the fear of precipitating paralysis in a child affected by anterior poliomyelitis (Martin, 1950; McCloskey, 1950; Geffen, 1950; Bradford Hill and Knowelden, 1950) the use of irritant vaccines containing alum is being discontinued. The problem of whether saline vaccines are sufficiently potent antigenically with regard to each of the three constituents, pertussis, diphtheria and tetanus, must therefore be considered. It was with this problem in mind that the following investigation was undertaken.

Infants attending a routine follow-up clinic in the University Department of Child Health in Manchester were immunized with one of two vaccines, each comparable in the antigenic content of pertussis, diphtheria and tetanus, but one was in saline suspension and the other contained aluminium phosphate. Three injections were given to each infant at monthly intervals, the first being given when the infant was about 3 months old. Blood was taken by venipuncture one month after the third injection and antibody estimations were carried out, pertussis agglutinins, diphtheria antitoxin and tetanus antitoxin being measured. The results obtained are shown in Table 1.

The results show considerable individual variation

TABLE 1
RESULTS WITH PLAIN AND ALUM-CONTAINING VACCINES

	Pertussis Agglutination Titre	Diphtheria Antitoxin (units/ml.)	Tetanus Antitoxin (units/ml.)
Alum			
1	1/64	0·13	0·40
2	1/64	0·13	0·10
3	1/128	1·35	0·60
4	<1/16	0·525	0·80
5	1/128	0·68	0·10
6	1/512	3·60	0·60
7	1/64	1·05	0·60
8	1/128	0·53	0·60
9	1/32	1·40	4·0
10	1/1,024	0·70	1·00
11	1/16	1·05	0·9
12	1/512	1·05	0·45
13	1/64	0·175	1·05
14	1/16	0·044	0·05
15	1/512	0·525	1·00
16	1/512	1·05	0·80
17	1/128	0·375	0·80
18	1/16	1·20	2·0
19	1/128	0·263	0·10
Plain			
1	1/32	0·14	0·02
2	1/16	0·044	0·01
3	<1/16	0·70	0·20
4	<1/16	1·35	0·10
5	1/128	2·10	0·10
6	<1/16	0·70	0·10
7	<1/16	0·13	0·10
8	<1/16	0·24	0·40
9	1/64	0·13	0·10
10	1/1,024	1·05	1·5
11	No serum	0·525	0·45
12	1/1,024	0·525	2·0
13	1/512	2·40	1·60
14	<1/16	0·05	<0·02
15	1/16	4·20	2·00
16	<1/16	1·05	0·30
17	1/64	0·125	0·20
18	<1/16	1·80	1·60
19	<1/16	1·80	1·00
20	<1/16	1·80	2·00
21	1/16	1·50	2·00
22	<1/16	<0·0035	0·10

TABLE 2

Vaccine	No. Tested	No. of Children with Diphtheria Antitoxin Level of					
		<0·5	0·5–1·0	1·0–2·5	2·5–5·0	5·0–10·0	10·0–20
A	22	8	4	9	1	—	—
B	19	6	5	7	1	—	—
C	34	0	1	2	9	15	7

TABLE 3

Vaccine	No. Tested	No. of Children with Tetanus Antitoxin Level of			
		<1·0	1·0–5·0	5·0–10·0	10
A	22	14	8	—	—
B	19	14	5	—	—
C	33	0	17	14	2

TABLE 4

Vaccine	No. Tested	No. of Children with Pertussis Agglutination Titre of									
		<1/16	1/16	1/32	1/64	1/128	1/256	1/512	1/1,000	1/2,000	1/4,000
A	21	11	3	1	2	1	0	1	2		
B	19	1	3	1	4	5	0	4	1		
C	35	2	0	0	1	1	2	4	10	11	4

A = Plain vaccine at monthly intervals. B = Alum vaccine at monthly intervals.
C = Alum vaccine; third injection four to five months after second.

in response but if each type of vaccine is considered, together with response to the separate constituents, certain points of interest arise.

The alum-containing vaccine produced what is probably an immune level of antibody to the diphtheria and tetanus toxins. It also produced a measurable level of agglutinating antibody to pertussis in all but one child. On the other hand with the plain vaccine, although the level of diphtheria and tetanus antitoxins produced is probably adequate in all but one child, the production of agglutinating antibody to pertussis does not seem so satisfactory; of the 22 children in this group, 11 (50%) did not produce a measurable level of agglutinating antibody.

If we ignore the difference in titre of diphtheria and tetanus antitoxin in the two groups, as the levels in almost every group are sufficient to promise immunity, the response to pertussis agglutinogen should be studied. Here an alarming situation has arisen—if the power to produce agglutinins bears any relationship to the power to produce immunity. Although all but one of the children (approximately 95%) given the alum-containing vaccine responded, 50% of the children given the plain vaccine did not. Have we any proof of an immune response as an isolated reaction to a whole pertussis antigen? Until such a demonstration has been made there can be no justification for using an antigen of such reduced potency unless the dangers attached to the mineral-containing vaccine are excessive. The danger of local reaction is slight if a correct technique is used and the occasional abscess and pain are not sufficiently serious to justify the discontinuing of the alum vaccines. What then of the dangers of poliomyelitis? The policy of health authorities at present is to discontinue all immunization procedures during an epidemic and this is probably the wisest plan (Ministry of Health, 1952). Although less irritant injections are not so likely to cause paralysis the danger still exists in a minor degree. Surely another danger may be produced by using an uncertain vaccine, namely one of false security against pertussis, a disease less publicized than poliomyelitis but with a high morbidity of its own. In addition, the use of such an inadequate antigen may bring discredit on immunization in general.

A further point of interest arises when the results obtained in this series are compared with a previously published series (Feldman, 1954) in which the third injection was delayed until four to five months after the second. The antibody levels when obtained were greatly in excess of those in the present series with the three injections given at monthly intervals. The vaccine used in this previous trial differed in containing twice as much aluminium phosphate as the mineral-containing vaccine used in the present series. However, a comparison of results is justifiable as it is unlikely that the marked difference in antibody titre is entirely due to this and is much more probably due to the delayed third injection. Tables 2, 3 and 4 give a comparison of the titres

obtained with the two vaccines used in the present trial (A, plain vaccine, B, aluminium phosphate vaccine), in which the three injections were given at monthly intervals, and the titres obtained in the previous trial in which a vaccine (C) containing aluminium phosphate was used. In this last series the first injection was given at about 3 months of age, the second a month later and the third four to five months after the second. It will be seen that a higher mean titre is obtained to all three constituents when the third injection is delayed.

Summary

Results are presented obtained when comparable pertussis, diphtheria and tetanus triple antigens, one in saline suspension and the other containing a mineral carrier, were used in the immunization of two similar groups of infants.

Fifty per cent. of infants given the saline antigen failed to produce measurable titres of pertussis agglutinin.

The reasons for the use of plain antigens are discussed and considered insufficient to warrant their preference to the more potent alum-containing antigen.

Delaying the third injection until four or five months after the second produces a higher mean response to all three constituents.

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