Efficiency of Antibody Response in the Infant Under Three Months of Age

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For a long time, it has been taken for granted that the new-born infant is incapable of response of any significant nature to antigenic stimuli given for the purpose of immunization. Because of this and the wide spread belief that the infant was readily protected by antibodies passively transferred from the mother in utero, the importance of immunization before three months, even before six months, was belittled. The Yearbook of Pediatrics, 1949, refers to Hirszfeld's work in 1926 as the original source for such widespread belief, while Dr. Stewart, in an article in the Nova Scotia Medical Bulletin, January, 1951, (I) goes back to the work of Park (2) in 1922, who was certainly one of the pioneers in early immunization.

In scanning the literature, it seems fairly evident that early immunization is both possible and practical. The best argument for early immunization is for protection against whooping cough, a disease in which 75-80 per cent of all deaths occur in children under one year of age, most of these under six months (I). Certainly other reasons could be cited in favor of immunization before the presently accepted three months of age.

An interesting study was reported by di Sant'Agnese (3) which gives a good introduction to the topic. He makes reference to the accepted beliefs, and comments upon the experience data and electrophoretic studies on plasma proteins in animals. The data supports these theories by showing a quantitative and even a qualitative difference between antibodies produced by newly-born animals and by more mature members of the same species. In his article, he sets out to find:

1. What antibody responses newborn infants have to injection of known antigen.
2. What is the influence of age on antibody production.
3. What is the earliest age at which routine immunization can be attempted with assurance of success.

The material chosen for inoculation was a triple combined vaccine prepared by the Cutter Laboratory, called "Alhydrox". In this material, 20 billion **Hemophilus pertussis** organisms per ml. are added to aluminum hydroxide, absorbed tetanus and diphtheria toxids.

The study was done on 189 full term infants—three deep subcutaneous or intramuscular injections at one month intervals, as follows:

0.5 ml. at 1 week
1.0 ml. at 5 weeks
1.0 ml. at 9 weeks

(a) Serum agglutinins against **H. pertussis**-

Before: 98 per cent of 144 tested had no agglutinins. At 13 weeks, one month after the third injection, only 30 per cent of 125 had no agglutinins; 54.4 per cent had a titer of 1:400 or higher, which according to Sako (4) yielded complete protection against exposure to pertussis. However, the level needed for protection is still not certain. Sako has shown a number of patients with low or even no titers after prophylactic inoculation to be immune on exposure, and theorizes that although there are no circulating antibodies, the tissues have been sensitized and respond when in contact with the antigen as if it were a booster dose.

(b) Tetanus antitoxin—

Before: 15 per cent of 156 tested had appreciable antitoxin titers.

At 13 weeks, all of 128 patients had more than the protective titer of 0.1 Units per mls. of serum. 92 per cent had more than 1 Unit per ml.

(c) Diphtheria antitoxin—

0.003 Units per ml. of serum was considered to offer complete protection.

Before: of 168 infants seven days after birth 58.5 per cent had a "protective" titer. 12 per cent had more that 1 Unit per ml. At 13 weeks, 84.6 per cent of 123 had a "protective" titer. Only 20 per cent had more than 1 Unit per ml. Di Sant'Agnese comments that part of the injected toxoid was neutralized by circulating antitoxin, yet enough reached the tissues to produce satisfactory immunization.

Influence of age on antibody production:

With pertussis, the response was better in the older group than in the newborn group. The reason is given that since passive immunity to pertussis was not present at birth and therefore could not interfere with above immunization, the poorer response of newborn infants as compared with older children must be attributed solely to immaturity of the immune mechanisms.

With tetanus, the results were equally good in both age groups because of the great antigenic capacity of the tetanus toxoid. He suggests that this overcomes the immature immune mechanisms.

With diphtheria, the relatively poor showing of the newborn may be attributed at least partly to the presence of placentally transmitted passive diphtheria antitoxin. The toxoid was only partially strong enough to overcome combined handicaps of tissue immaturity and existing passive immunity.

Di Sant'Agnese concluded that in the first months of life, the antibody response to antigen increases with advancing age. Although with diphtheria immunization the combined handicaps of antibody interference and tissue immaturity greatly limited the procedure, a significant degree of protection was possible with pertussis vaccine, and especially with tetanus toxoid. He felt that in some cases a sufficient potent antigenic stimulus could overcome the tissue immaturity, but that more work as to evaluation of the level required for clinical protection was needed before immunization in the newborn could be advocated as a routine procedure.

Park's work in 1922 was done with toxin-antitoxin mixtures. Infants were injected three ,eight, and eleven days after birth, and 100 of those were Schick tested at the age of one year. Only 52 per cent had a Schick negative test which was about equivalent to that given by a similar group of untreated infants of the same age. It is evident that the combined effect of immature cells and over-neutralization of the toxin-antitoxin mixture, because of the passive immunity of the mother (the number of immune mothers then being high), prevented any appreciable response. It was this early work that created the widespread belief in the inefficiency of the infant's tissues to respond to stimuli, no matter how strong.

However, later work was to show:

1. The per cent of infants with passively transferred antibodies was rapidly decreasing.

2. Diphtheria toxoid was not inhibited to the same extent by such antibodies, but some inhibition does occur.

Cooke and associates (5) offered more evidence in the unravelling of this problem in a study on 5,028 white and negro infants one to fourteen months of age, most under six months. With tetanus toxoid, the results were as good as previous workers had obtained. With diphtheria toxoid, results were good where there was no passive immunity, but where there were even minor titers of antibodies, the results were poor. Interference with antibody production was due to the presence of recognizable passive immunity. Even small amounts of demonstrable antitoxin may prevent the process. Cooke further makes the point that fewer adults are Schick negative so there is less tendency for interference by passively transferred antibodies. According to Bo Vahlquist (7), the level of immunity in the adult population of 85 per cent as quoted in 1916 is no longer valid. In fact, the level lies between about 30-50 per cent and may be somewhat lower. In 1945, Vahlquist and Persson found an incidence of antitoxin in infants under three months of only 16 per cent.

Sako (4) claimed practicality of pertussis vaccination. His results were as good with infants less than three months as with older children. He stated that prolonged antigenic stimulation as afforded by alum precipation was necessary for efficient antibody production. Early investigators (6) did similar work but their technique for measuring the response was poor.

Bo Vahlquist (7) added further evidence with respect to diphtheria immunization.

He found that at age 2 to 3 months, the effect of immunization is quite comparable to that in children 6 to 8 months of age, older children, and adults, where there was no passive immunity. He also showed however, that a level of passively acquired antibodies greater than 0.1 Units per mls. of serum apparently inhibited entirely the effect of toxoid in the dosage used. Therefore, he suggested early diphtheria vaccination where the incidence and hence likelihood of passive immunity is low and putting off vaccination until six months of age where natural immunity was more likely.

He claims that workers underestimated the ability of infants to produce antibodies because of the following reasons:

1. The inhibitory effect of passively transferred antibodies was not known.

2. Delayed antibody response was not recognized, that is, a slower ex-foliation of the antibodies into the bloodstream. (see below)

3. The results of immunization were compared by other workers with those of older children and adults. These, even though Schick positive, may have been under influence of natural antigen previously whereby the injection of toxoid had the effect of a booster dose.

4. The non-precipitated toxoids formerly used were antigenically weaker and of shorter antigenic duration—this is especially important in the young infant.

Studies on other immunization procedures.

Gaisford and Griffiths (8) found in BCG vaccination that the effective dose was 0.1 mls. and that results were as good in the young infants as in the adults. Conversions to the Mantoux tuberculin test occurred in the range of 16 days to 10 weeks, the time varying with the dose. This correlated with Wallgren's work in 1950 that suggested that tuberculin sensitivity could not be expected until 10 to 12 weeks after immunization as against 4 to 6 weeks as results showed when done in later childhood.

Similarly, in the International Medical Digest (9) a study shows a decrease in the incidence of tuberculosis following vaccination in the newborn.

Without vaccination: One could expect decrease of 27.4%.

With vaccination: the decrease was 55.9% These results, when analyzed, are statistically significant.

Another study (10) shows a lower incidence of tuberculosis in infants exposed to it who were vaccinated at birth with BCG, but the results were good only where the exposure followed conversion to the Mantoux test.

With respect to polio (11) it was shown that a satisfactory antibody response was possible with injections given to infants as young as six weeks of age, even when mixed with pertussis vaccine or DPT mixture. Also, the existence of maternally transmitted antibodies at the time of immunization had no apparent influence on the production or persistence of activity formed antibodies.

Smallpox immunization has been performed in England at six weeks of age for quite a few years with good success.

I have not found evidence which formulates an antibody response in the premature infant, but it is commonly stated that its immune mechanisms are more immature than those of the full-term infant. There seems to be little reason to doubt this, but successful BCG vaccination has been performed in the young premature infant (12).

SUMMARY AND CONCLUSIONS:

1. Immunization in the infant under three months of age is not ineffective and can be carried out practically.

2. Early immunization against pertussis can play a major role in decreasing the number of deaths per year from whooping cough. Early immunization against tetanus will lower the need of antitoxin injections in early childhood, since toxoid can be administered instead, and the chance of sensitization by serum injections will be lessened. Early immunization against tuberculosis, polio, and against smallpox will also be possible and practical.

3. Early immunization against diphtheria can be carried out taking into consideration the views of Vahlquist.

4. In studies where combined antigens were used, it had previously been proved that combinations had no influence on the effect of any of the antigens, even in the case of polio(11).

5. In the Washington University Clinic, the following immunization procedure is carried out:

Quadruple vaccine at 6, 9, and 12 weeks. Diphtheria and tetanus toxoids at 7 and 9 months.

(It is generally believed that immunization against tetanus is unimportant in the infant, but I have suggested otherwise above. It is widely accepted that

there is less susceptibility for diphtheria in the young infant—this is generally true, but the argument of antibody interference is not as strong as it once was.)

It is feasible that the following immunization procedure may soon be carried out with success:

BCG vaccination in the newborn.

Quadruple vaccine at 6, 9, and 12 weeks
Smallpox vaccination at 6 months as is customary.

One should remember that such a schedule will require earlier booster administration, and that a booster at about 7 months may, with respect to diphtheria, be acting as the initial administration (where antibory interference has occurred). These procedures can be carried out successfully with a minimum of difficulty.

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