NERVOUS REACTIONS AND ANTIBODY RESPONSE
IN INFANTS, FOLLOWING THE USE OF YELLOW-FEVER
IMMUNIZING VACCINES

by

G. Stuart, M.D.

1. Is anti-yellow-fever vaccination of children under one year of age necessary or desirable?

This problem involves consideration of two questions: (1) is there greater risk of meningo-encephalitic reactions among infants who are vaccinated within their first 12 months of life than there is among children of one year and above; and (2) is the immunity response to vaccination in the under-ones sufficient to ensure protection and to justify their being issued with an international certificate of vaccination against yellow fever which has a validity of 6 years?

Is there greater risk of post-vaccination encephalitis among the under-ones?

While it seems clear, from a perusal of the relevant literature, that reactions of a meningo-encephalitic nature tend to occur most frequently among the lower age groups, the number of cases recorded as belonging to the under-one sub-group is too small to permit generalization on this point. Thus, following the use of the French neurotropic virus vaccine in Costa Rica during 1951, among 12 cases in children between the ages of 9 months and 13 years, only one was under the age of one year; while in Nigeria during January 1952, when 19,358 children under 10 years old were vaccinated, of the 73 cases of encephalitis recorded, 33 fell within the age-group 0-2 years, but the incidence among the under-ones is not specified. Again, following the use of 17D virus vaccine in Brazil during 1941, there occurred, during a fully controlled field trial in Southern Minas Gerais, 5 cases of meningo-encephalitis among 1,681 children in the age-group 1-4 years, but in none of these cases was the exact age mentioned.
Now, because of its enhanced neurotropism, the potential hazards attendant upon the use of French neurotropic virus vaccine for, in particular, the immunization of children have been stressed by, among others, THEILER and WHITMAN (1935). Bearing this in mind, the WHO Expert Committee on Quarantine took the view in 1947 that for the safe immunization of very young children only 17D virus vaccine should be employed.

In this connexion, although a number of cases of encephalitis following the use of 17D vaccine in Brazil has been reported by FOX, LENNETTE et al. (1942) as having occurred among adults and children in 1941, the vaccine then employed had been prepared from a substrain of the virus which, during a very small number of subcultures away from the main stem, proved to have undergone a sudden alteration in character and acquired encephalitogenic properties. To preclude the possibility of recurrence of such serious nervous reactions, the technique of 17D vaccine preparation was, in 1941, altered so that the vaccines used were initiated from primary and secondary seed lots of known character. The standardization of 17D vaccine preparation, following the adoption of this "seed lot system", achieved the desired result: since 1942 no case of encephalitis following the administration of 17D has been recorded in the literature.

In a personal communication dated 22 June 1955, however, Dr. P. LEPINE of the Pasteur Institute, Paris, expresses himself as being unable to agree that the use of 17D vaccine is never concerned in the production of meningo-encephalitic reactions, and cites, in support of his contention, the following instances which have come under his own observation within the past two years:

- 1 case among 800 children of from 6 months to one year of age; and
- 4 cases among 1,000 children of from birth to 6 months old.

All 5 cases recovered completely.

Among 40,000 adults vaccinated during the same period, no case of meningo-encephalitis occurred.

In this connexion it is stated that all these children and adults had been immunized with the same vaccine - a vaccine prepared from a 17D (Rockefeller) strain and rigorously titrated prior to use.
The main particulars of the 5 cases cited are shown in the subjoined Table.

**Summary of observations on 5 encephalo-myelitic reactions following vaccination with 1/100 vaccine (1951-53) on the Pasteur Institute, Paris**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Incubation period</th>
<th>Clinical picture</th>
<th>Duration</th>
<th>Result of sero-protection test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>7 months</td>
<td>F.</td>
<td>19 days</td>
<td>Convulsive seizures; then hemiplegia. Cerebro-spinal fluid: 12 cells per 1 cm³</td>
<td>48 hours</td>
<td>++ = 250LD&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>2.</td>
<td>1½ mths.</td>
<td>M.</td>
<td>11 days</td>
<td>Repeated convulsive seizures (6 per day) - left-sided</td>
<td>48 hours</td>
<td>not tested</td>
</tr>
<tr>
<td>3.</td>
<td>1 month</td>
<td>M.</td>
<td>12 days</td>
<td>Repeated convulsive seizures</td>
<td>48 hours</td>
<td>Negative: = less than 250LD&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>4.</td>
<td>6 months</td>
<td>M.</td>
<td>12 days</td>
<td>Certain signs of encephalitis; temperature 38-39°C; vomiting; S.S. fluid: 120 cells per 1 cm³ Treated with streptomycin; spectacular improvement.</td>
<td>5 days</td>
<td>not tested</td>
</tr>
<tr>
<td>5.</td>
<td>4 months</td>
<td>F.</td>
<td>10 days</td>
<td>Hospitalized for high temperature (40°C). Lumbar puncture on 13th day (slight tension over the fontanelle). C.S.F.: 150 cells per 1 cm³ Return to normal on 16th day, without therapeutic treatment.</td>
<td>5 days</td>
<td>blood taken: not completed</td>
</tr>
</tbody>
</table>
In Dr. Lépine's view a distinction must be drawn between case No.1 and the other 4 cases. Case No.1 was a child of the black race, was over 6 months' old and developed a satisfactory immunity response to the vaccination; in this case the period between vaccination and onset of encephalitic signs was 19 days.

In contrast with the experience of Dr. Lépine, that of STEFANOPULO and DUVOLON (1947) may be cited. The last-named authors, in a review of their 10 years experience with yellow-fever immunization at the Pasteur Institute, Paris (1936-46), drew attention to the lack of harmful reactions following the use of 17D. They observed no nervous reactions in 2,470 children of from 15 days to 10 years' old and compared this with the occasionally severe nervous reactions which had followed the use of French neurotropic virus vaccine in young children.

2. Is the immunity response to vaccination in children under one year of age sufficient to ensure their protection against yellow fever and to justify their being issued with an international certificate of vaccination against yellow fever which has a validity of 6 years?

The possibility that the response of an infant under one year of age to a yellow-fever vaccination may be negligible has from time to time been suggested, but a review of the literature fails to uncover data to confirm or refute this suggestion.

It is true that, following a mass vaccination with 17D virus of the total population (145,000) of the Toro District in Western Uganda in 1941, when individuals of all ages from babies at the breast to the elderly were vaccinated, SMITHBURN and MAHFFY (1945) reported to the effect that "after the mass inoculations the incidence of immunity was of quite even distribution ..... and that the rate in children was as high as that in adults. Furthermore, 3 years after completion of the vaccination programme, the children retained their immunity as well as the adults". These authors also concluded that "the validity of the vaccination certificate may safely be extended beyond 3 years, without reference to the age of the vaccinated person". It is also true that post-vaccination surveys made by DICK and SMITHBURN (1949) in 1946 and 1947 on the inhabitants of certain localities within the above-mentioned vaccination area - localities at
about an altitude of 5,000 feet and where no yellow fever had occurred - found among 33 children of the 5 or 6-9 years' age-group, who had been vaccinated 5 or 6 years previously, 28 immunes (84.8%) and, on more detailed analysis of these figures for the age-group in question, that 16 out of 21 tested were immune 5 years after vaccination (76.2%) and 12 out of 12 tested (100%) 6 years after vaccination. From the results of their surveys these authors concluded that "there is no significant difference either in the percentage developing immunity or in the duration of the immune response when children are compared with adults".

Again, the studies of ANDERSON and GAST GALVIS (1947) in Colombo show no significant difference in the immune response of children and adults. Results of neutralization tests in sera obtained from residents of 4 Colombian towns 5 years after vaccination with 17D showed 579 out of 623 vaccinated to have protective antibody (95%). Because of the view expressed by FOX and CABRAL (1943) that young children give a poorer response to vaccination than do adults, sera of the age-group 6-9 years received particular attention; in that group 59 of the 65 vaccinated and tested contained neutralizing antibody (91%). 20 of these 65 sera were taken from children under 3 years of age at the time of their vaccination; of these, 16 (80%) contained antibodies. Of the 45 sera from children who were from 3-4 years' old at the time of vaccination, 43 (96%) contained antibodies. These authors conclude, however, that, "in view of the small groups compared, the difference is not statistically significant and that the response of children under 3 years of age does not materially differ from that of older children or adults".

In connexion with the question under consideration, however, it will be noted that in none of the three articles mentioned above is any specific information provided on the immunity response to vaccination of the 0-1 year age-group or to the duration of such immunity as may have been conferred. Moreover this comment applies also to the results of 17D vaccination published by FOX and CABRAL (1943); from their studies in Southern Brazil, these authors found that in the case of populations largely or entirely composed of young children the early response to vaccination was much less satisfactory than in populations comprising mainly adults and a more rapid decline in the immune level was apparent. The age-groups on which such observations were made, however, were: 5-9, 10-14, 15-19, 20-29, and
30+ years. In respect of vaccinations carried out on individuals of these age-groups, FOX, KOSSOBUDSKII and FONSECA DA CUNHA (1943) stated that evidence was adduced that the immune response to 17D virus in individuals up to 14 years is directly related to age, the average protective capacity of the sera increasing with the age of the donors. Later, FOX, FONSECA DA CUNHA and KOSSOBUDSKII (1948), reviewing the results and extending the investigations recorded in the two previous papers, found that the differences between the results with sera of children in the 5-14 years' age-group and those of adults in the 15 years and over age-group were not statistically significant.

As previously stated, therefore, it is quite possible that the response of a very young infant to a yellow-fever vaccination might be negligible, but no data are to be found in the available literature which could confirm or refute the hypothesis. The answer to the question could be provided only by the results of a carefully planned experiment of adequate size.

While this experiment is being carried out, (unless in addition to the one now provided by Dr. Lépine - a sero-protection test on an infant one month old showing a negative result - convincing figures in support of the hypothesis are in the meantime produced), some interim arrangements may be considered to be essential. If so, then the operative considerations would seem to be:

1. it is not possible to exclude from vaccination all infants under one year old;
2. unprotected infants are, so far as it can be learned, liable to contract and carry yellow fever in the same way as adults;
3. inoculation of infants under one year old probably confers limited protection; and
4. inoculation of infants over one year old probably confers protection which will last the accepted six years.

In the circumstances it has been suggested that the only solution to the problem - admittedly not a very satisfactory one - is to have a special certificate for the under-ones, valid for one year, and to require these infants to be revaccinated at the end of that time, when they can be given a normal six years' certificate.
The only justification for postponing vaccination until the child is over one year old, and allowing those under that age to travel unprotected, would be the production of irrefutable evidence that infants under one cannot contract yellow fever.

"So far as is known, however, man is naturally more or less uniformly susceptible to infection with yellow-fever virus, with the possible exception of infants born of immune mothers; such infants may be immune for the first few months of their lives." (TAYLOR, 1951). "Aëdes aegypti-transmitted yellow fever is generally acquired indoors, tends to involve all non-immunes of all ages living in infected houses ...." (SOPER, 1958). "Inapparent infections may occur in babies, who are losing the passive immunity bestowed upon them by immune mothers and who are infected with exactly that amount of virus which "vaccinates" them without symptoms." (AUSTIN KERR, 1951).

This transmission of a transitory immunity from the immune mother to her offspring naturally raises the question of whether or not very young infants belonging to this category require vaccination. If the mother is immune, her offspring will probably have sufficient immunity to result in protection for some weeks or a few months. [The longest demonstrated persistence of the inherited immunity has been 6 months in children.] However, the time of disappearance of the antibody is variable and its presence can be determined only by test. If the child is living in an endemic area, the administration of the vaccine should not be delayed more than about 2 months, or perhaps not at all during epidemics. The presence of the antibody in the infant's blood would render the vaccine ineffectual; yet to withhold the vaccine might be hazardous in the event that the antibody had disappeared." (SMITHBURN, 1951).
REFERENCES


LEPINE, P. (1953). Personal communication.


