

## SCHICK REACTIONS IN RECENTLY CONFINED WOMEN AND THEIR NEW-BORN INFANTS

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It has long been known that a relative immunity to diphtheria can be found in the new-born. This congenital immunity is passive and is supposed to be due to transmission of the mother's antitoxin to the foetus through the umbilical vein. Numerous investigations with the Schick reaction have been carried out with a view to determining the extent to which this passive immunity to diphtheria occurs in the new-born. These investigations have, however, led to but little unanimity.

It has been maintained that Schick reaction in the new-born is uncertain and is no reliable index of immunity. Determinations of the blood's antitoxin titre have shown that numerous new-born infants with a negative Schick reaction had a titre under  $\frac{1}{30}$  unit of antitoxin per c.c. of blood serum. They should, therefore, be liable to contract diphtheria. Cases have also been recorded of deaths from diphtheria among new-born infants with a negative Schick reaction. On the other hand, Messeloff & Karsh (1932) have in no instance found a child with a negative reaction to the Schick test with no antitoxin in the blood. Of the children with a negative Schick reaction 94% had at least  $\frac{1}{30}$  unit of antitoxin per c.c. of serum.

Several large statistics concerned with the Schick reaction in the new-born have shown that most of them were negative reactors. These investigations have, however, for the most part been carried out in the lower social strata of large towns in which the overwhelming majority also of the mothers were negative Schick reactors. In an earlier study (Vogelsang & Kryvi, 1945) dealing with 3000 adults in Bergen whose population is a little over 100,000, it was found that 67% gave a positive Schick reaction. This study included 147 recently confined women, 105 of whom (71%) were Schick-positive. In view of this comparatively great number of Schick-positive puerperal women, such a material ought to be well suited for an investigation of the value of the Schick reaction in puerperal mothers and their new-born infants. In connexion with this study the Schick reaction has therefore been carried out on 500 puerperal women and their new-born

infants. The results of this investigation are as follows.

### MATERIAL AND PROCEDURE

The investigation was carried out at the Hospital for Gynaecology and Obstetrics in Bergen. The confinement cases admitted to this maternity hospital are recruited from nearly all the social strata in Bergen and the neighbouring country districts in western Norway.

To save time and to avoid confusion of the toxin with the control dilution, the investigation was carried out by two persons, one of whom gave the toxin by intradermal injection into the flexor surface of the right forearm, whereas the other injected the corresponding control dilution into the left forearm. The needle was changed at every injection.

The skin of the new-born is tougher than that of older children and adults. It is therefore comparatively difficult to give the new-born an intradermal injection. Special care has therefore been taken with the technique of the intradermal injection of 0.1 c.c. of Schick toxin.

The test was carried out at the day of birth or in the course of the three following days, the reaction being read off from 2 to 4 days later. The toxin and the control dilution from the State Serum Institute in Copenhagen were employed.

### RESULTS

This study concerns 500 mothers and their infants. There were two cases of twins, but because, as will be discussed later, both pairs gave the same reaction, only one of each pair was included in the analysis.

The ages of the mothers ranged from 17 to 45 years. In 288 cases (58%) their ages ranged from 25 to 34 years. In 111 cases (22%) they were over, and in 101 cases (20%) they were under this age.

In the case of 451 mothers and their infants (90%) the results were the same for both mother

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and child, the reaction being positive for both in 338 cases (68%) and negative in 113 (22%). In 49 cases (10%) the results were at variance. In 37 of these cases the mother gave a positive and her child gave a negative reaction. In 12 cases this state of affairs was reversed, the mother giving a negative and her child a positive reaction. Altogether, 375 of the mothers were positive reactors (75%) and 350 of their children (70%) were so also. The infants of all the mothers giving a positive reaction were in nine cases out of ten themselves positive reactors.

In several of the cases in which the mother's Schick reaction was positive and her child's reaction was negative, the reaction was but little marked. With a view to a closer study of this phenomenon, the extent of the area of the reaction in both mother

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an area of 5-10 mm. in diameter, it will be seen that the contradictory findings rise in frequency as indicated in Table 2.

According to this grouping, 427 mothers and their infants (85%) gave identical results, the reactions being positive in both the mother and her child in 296 cases (59%), whereas in 131 cases (26%) the reaction was negative in both. In 73 cases (15%) the Schick reaction gave contradictory results. In 67 of these cases the mother's reaction was positive, while her child's reaction was negative; in six cases this state of affairs was reversed, the mothers being negative and their children being positive reactors. According to the same calculation, the mothers gave a positive reaction in altogether 363 cases (73%) and their children did so in 302 cases (60%). In all the cases in which the

Table 1. *Comparison of reactions to Schick test in mothers and their new-born infants in 500 cases*

Mothers' reaction	Infants' reaction				Totals
	++	+	±	÷	
++	2	58	44	5	109
+	7	106	55	15	183
±	—	33	33	17	83
÷	—	2	10	113	125
Totals	9	199	142	150	500

- ++ Area of reaction measuring 20 mm. or more in diameter.
- + Area of reaction measuring 10-20 mm. in diameter.
- ± Area of reaction measuring less than 10 mm. in diameter.

and child was measured. This measurement was carried out in the long axis of the arm and at right angles to it.

Table 1 shows the results of this measurement, a reaction area of 20 mm. or more in diameter being indicated by ++, an area of 10-20 mm. by +, and an area less than 10 mm. by ±. When the mothers' reaction was as markedly positive as ++, 95% of their children gave a positive reaction. When the mothers' reaction was moderately positive (+), then 92% of their children gave a positive reaction. When, however, the mothers' positive reaction was as weak as ±, only 80% of their children gave a positive reaction.

However, in several cases the reaction was so weak both in the mother and her child that it measured less than 5 mm. in diameter. Even though these weak positive reactions could be distinguished from the small nodular areas occasionally to be seen as the result of a needle prick, it is doubtful whether they ought to be regarded as positive reactions. If we group as ± only the reactions with

Table 2. *Comparison of reactions to Schick test in mothers and their new-born infants in 500 cases*

Mothers' reaction	Infants' reaction				Totals
	++	+	±	÷	
++	2	58	37	12	109
+	7	106	41	29	183
±	—	30	15	26	71
÷	—	2	4	131	137
Totals	9	196	97	198	500

- ++ Area of reaction measuring 20 mm. or more in diameter.
- + Area of reaction measuring 10-20 mm. in diameter.
- ± Area of reaction measuring 5-10 mm. in diameter.

mothers gave a positive reaction, 82% of their children did so also.

When, according to the same grouping, the mothers showed a strong positive reaction (++) , 89% of their children gave a positive reaction. When the reaction of the mothers was moderately positive (+), 84% of their children gave a positive reaction. When, however, the mothers showed a faintly positive reaction (±), only 63% of their children gave a positive reaction.

As a rule Schick reaction was much more marked in the mothers than in their children. Of the 500 mothers, 109 belonged to group ++, 183 to + and 71 to ±. The corresponding figures for their children were 9 (++) , 196 (+) and 97 (±).

In two cases the mothers gave a vesicular reaction. One of them, aged 45, gave a reaction with an area of 25 by 25 mm., whilst her child's reaction measured 7 by 7 mm. The other woman, aged 25, gave a reaction whose area measured 35 by 28 mm., whereas her child's insignificant reaction measured 4 by 4 mm. and was recorded in Table 2 as negative.

The strongest reaction observed in any child measured 30 by 23 mm. The reaction of the mother, aged 41, measured 16 by 13 mm. In six cases the children gave a positive reaction while their mothers' was negative. If one also takes into consideration the quite weak reactions with an area under 5 mm. (Table 1), there were 12 children giving a positive reaction while the reaction of their mothers was negative. In two of these cases (6 and 12 respectively) the reaction was moderately positive (+), measuring 10 by 10 mm. and 10 by 8 mm. respectively. In the latter case there was also a pseudo-reaction with an area of 5 by 5 mm. on the other arm. Apart from this case there was only one other child giving a pseudo-reaction which was slight and concerned both arms. In the four other cases in which the reaction was recorded as positive in the children but negative in their mothers (Table 2), the reactions were not very marked, being 5 by 3 mm., 5 by 4 mm., 7 by 5 mm., and 6 by 4 mm. respectively.

The two mothers who gave birth to twins showed a positive reaction, as did the twins themselves (Table 3).

Table 3. Comparison of reactions to Schick test in mothers and their twins in two cases

Age	Mothers' Reaction (mm.)	Twins' reaction (mm.)	
		1	2
31	20 × 10	7 × 6	8 × 4
32	18 × 15	9 × 8	8 × 6

Several of the mothers had previously been given injections of diphtheria toxoid. Seventeen mothers had undergone complete immunization against diphtheria with three injections of toxoid. Fourteen of them gave a negative reaction, as did their children. Three of them gave a positive reaction, as did two of their children; the third child was a negative reactor.

Of the 25 mothers who had received two injections of toxoid, 18 gave a negative reaction and so did the children. Among the remaining seven mothers whose reaction was still positive there were two whose children gave a negative reaction; the other five children were positive reactors.

Of the 13 mothers who had received only one injection of toxoid, nine were found to be negative reactors; their children were so also. The remaining four mothers were positive reactors, and of their children, one was a negative reactor and three were positive.

Comments

If the Schick reaction is taken to be positive when its diameter is 5 mm. or more, then 73 % of the mothers in this investigation showed themselves to be susceptible to diphtheria according to the verdict

of this reaction. Of the children whose mothers were positive reactors, 82 % gave a positive reaction. Thus, in most cases, the reaction of the children corresponded to that of the mothers. But 18 % of the children of mothers with a positive reaction showed a negative reaction. Such children were to be found with comparative frequency among mothers who had reacted feebly to the Schick test. Whereas 89 % of the children gave a positive reaction when their mothers showed a strong positive reaction, only 63 % of the children gave a positive reaction when the reaction of their mothers was faintly positive.

Kobak & Greengard (1932) have investigated the reactivity of the skin with reference to intradermal injections of various antigens, including diphtheria toxin given intradermally (Schick test dosage). While a large percentage of the mothers responded to intradermal injections of the antigens with an erythema extending from 3 to 4 cm., the overwhelming majority of their new-born infants gave either no reaction or an occasional slight reaction of about 1 cm. Usually the puerperal patient had a larger reaction than the pregnant patient, who in turn was found to exceed the non-pregnant woman in the responses of the skin. Thus, in comparing the reactivity of the skin of a new-born infant with that of its mother, one must bear in mind that one is dealing with extremes of sensitivity which appears to be greatest in the puerperal mother and least in her infant.

Germaine Dreyfus-Sée (1938) has shown that the tissues of infants less than 6 months old possess a special form of immunity which she has studied under the name of tissue immunity. She believes that it is on account of this immunity that it is rare to find diphtheritic membranes on the mucous membranes and skin of infants. She finds in her views an explanation for the special form of general diphtheritic poisoning to which infants are subject. The tissue immunity of the skin and mucous membrane can, to a certain extent, neutralize the action of diphtheria toxin.

These investigations are in conformity with the experimental investigations by Wadsworth & Hoppe (1931) into the neutralization or destruction of diphtheria toxin in guinea-pigs by tissue. Embryonic guinea-pig cardiac muscle tissue growing in cultures *in vitro* possesses the power of neutralizing, binding or destroying diphtheria toxin so that it is no longer toxic for normal guinea-pigs. Such neutralization takes place through the intervention of growing tissue and is a property which is lacking in similar surviving tissue not in a state of cultivation. Thus it appears that the living, growing cells of the tissues neutralize or destroy limited quantities of toxin. Only when the quantity of toxin exceeds a certain limit is its action injurious.

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As the tissues of the new-born infant are in active growth and closely resemble embryonic tissues, it may well be that they are capable of neutralizing or destroying small quantities of toxin. This neutralizing capacity of the tissues may explain the fact that mothers with a positive Schick reaction can give birth to Schick-negative infants.

It is natural to assume that the antitoxin content of a new-born infant is identical with that of its mother. If the mother, and therefore also her new-born infant, has little or no antitoxin in the blood, the mother will give a strongly positive Schick reaction, whereas the neutralizing capacity of the growing tissues of her new-born infant will result in some of the Schick toxin being neutralized or destroyed with resulting diminution of the reaction.

If the mother and her new-born infant have an amount of antitoxin in the blood which is below or at the level of the turning point of the Schick reaction, the mother will give a faintly positive Schick reaction. Her new-born infant, on the other hand, will possess not only the neutralizing property of antitoxin in the blood, but also the neutralizing or destructive property of growing tissues. The reaction of this infant may therefore be negative.

When a mother's Schick reaction is moderate or faintly positive, it may happen that her new-born infant gives a rapidly transitory Schick reaction which is positive after two or three days, but which has become negative as early as the fourth to the fifth day. Messeloff & Karsh (1932) have determined the antitoxin content of the blood serum in several such cases. They have found this type of reaction in persons having less than the usual  $\frac{1}{30}$  unit of antitoxin per c.c. of serum. Though they consider this transitional positive reaction to be of great theoretical importance, they hold it to be of little significance clinically. Such persons will be ready to neutralize any toxin produced at the beginning of an infection so that in the great majority of cases the disease will not reach the clinical stage. Should clinical symptoms develop, the course of the illness will be benign, even without specific treatment with antitoxin.

In our material there were several cases in which the new-born infant gave a positive reaction while the mother was negative. It is not easy to explain such a discrepancy. The same phenomenon has been observed in a few cases by other investigators. Such positive reactions in the new-born can hardly be interpreted as pseudo-reactions which would seem, on the whole, to be rare in the new-born. As a rule, this discrepancy was associated with a faintly positive reaction in the new-born infant. In two cases, however, the reaction was strong enough to

be classed as moderately positive (+). To be sure, in one of these cases there was a slight pseudo-reaction on the other arm.

Several of the mothers examined had been immunized by diphtheria toxoid. Whenever the immunized mother gave a negative Schick reaction, her new-born infant was also negative. Liebling, Youmans & Schmitz (1941) have found that negative mothers, actively immunized, showed a marked response in the formation of antitoxin, in some cases as much as 5000 times the pre-immunization level being reached. Infants born to the actively immunized mothers gave negative Schick tests and had an antitoxin level in most cases equal to that of the mothers at term.

As during the first months of life an infant is, as a rule, a poor active antitoxin producer, Schick-positive women ought to be immunized during pregnancy with diphtheria toxoid so as to increase the passive antitoxin content of the blood of their new-born infants. Such a precaution should prove an excellent preventive of diphtheria in infancy.

Liebling (1941) has followed a group of infants whose mothers had been actively immunized during pregnancy, and he has found that children born to actively immunized mothers presented a negative Schick reaction when 8-9 months old. When infants have reached this age or one year, they should be actively immunized with diphtheria toxoid.

### SUMMARY

The Schick test was carried out on 500 recently confined women and their new-born infants. The Schick reaction was positive in as many as 73% of the mothers and in 60% of their infants. The infants were positive reactors in 82% of all the cases in which their mothers were positive.

The reaction of the new-born infants was, as a rule, weaker than that of the mothers. It often happened that when the mother's reaction was faintly positive, her infant's reaction was negative.

When the mothers had been immunized with diphtheria toxoid, the overwhelming majority of both the mothers and their new-born infants were negative. Immunization of Schick-positive women with diphtheria toxoid during pregnancy is recommended as a preventive of diphtheria in infancy, as by this means the antitoxin level of the new-born infant can be raised.

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